Drinking Distilled Onset, course and treatment of alcohol use disorders in the general population Marlous Tuithof

Drinking Distilled

Onset, course and treatment of alcohol use disorders in the general population

Marlous Tuithof

Drinking Distilled

Onset, course and treatment of alcohol use disorders in the general population

Marlous Tuithof

This thesis was prepared at the Netherlands Institute of Mental Health and Addiction (Trimbos Institute) in Utrecht and the Department of Psychiatry at the Academic Medical Centre in Amsterdam.

The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) is conducted by the Netherlands Institute of Mental Health and Addiction (Trimbos Institute) in Utrecht. Financial support has been received from the Ministry of Health, Welfare and Sport, with additional support from the Netherlands Organization for Health Research and Development (ZonMw) and the Genetic Risk and Outcome of Psychosis (GROUP) investigators.

The research described in this thesis was supported by grant 31160201 from the Netherlands Organization of Health Research and Development (ZonMw), which is gratefully acknowledged.

ISBN	978-90-5253-758-0
Cover design	Esther Ris, www.proefschriftomslag.nl
Lay-out & print	Off Page

Drinking Distilled
Onset, course and treatment of alcohol use disorders in the general population

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 3 juli 2015, te 10:00 uur

door

Marlous Tuithof
geboren te Maarssen

Promotiecommissie

Promotores:	Prof. dr. W. van den Brink	Universiteit van Amsterdam
	Prof. dr. W.A.M. Vollebergh	Universiteit Utrecht
Copromotores:	Dr. M.L. ten Have	Trimbos-instituut
	Dr. ir. R. de Graaf	Trimbos-instituut
Overige leden:	Prof. dr. A.E. Kunst	Universiteit van Amsterdam
	Prof. dr. H. van de Mheen	Erasmus Universiteit Rotterdam
	Prof. dr. A.J. Oldehinkel	Rijksuniversiteit Groningen
	Prof. dr. B.W.J.H. Penninx	Vrije Universiteit Amsterdam
	Prof. dr. G.M. Schippers	Universiteit van Amsterdam
	Prof. dr. R.W.H.J. Wiers	Universiteit van Amsterdam

Faculteit der Geneeskunde

CONTENTS

Chapter 1

General introduction

BACKGROUND

Alcohol is the most frequently used drug in Western countries: about 85% of the adults in Europe drank alcohol in the past year [1] and according to Statistics Netherlands, Dutch drinkers consume on average one alcoholic drink every day [2]. The strong embedding of alcohol in society is marked by the central role of alcohol use in social interactions [3]. Common motives to drink are: to relax, to get a good or pleasant feeling, because it is fun or sociable, or because it is part of a celebration [4]. These positive aspects aside, important downsides of alcohol use should not be ignored: excessive alcohol use is probably more harmful for the individual and society than the use of most illicit drugs [5-7]. Although drinking is often considered a social convention, maladaptive drinking patterns can interfere substantially with social functioning, as well as with family life, career, school and with mental and physical health [8-10]. This interference may be indicative of the presence of an alcohol use disorder (see Tables 1.1 and 1.2). In the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), two alcohol use disorders are distinguished based on number and type of criteria: alcohol abuse (≥ 1 of 4 criteria) and dependence (≥ 3 of 7 criteria) [11]. The recently introduced fifth edition of the DSM defines a single alcohol use disorder based on a combination of DSM-IV abuse and dependence criteria (≥ 2 of 11 criteria) with different levels of severity depending on the number of criteria that are met (mild: 2-3 criteria; moderate: 4-5 criteria; severe: ≥ 6 criteria) [12].

Alcohol use disorders affect approximately 76 million people worldwide [13] and about half a million people in the Netherlands [14]. Particularly alcohol dependence is associated with a high disease burden [10;15] and with mortality [16]: about two-thirds of all alcohol-related mortality is caused by the 4% of alcohol users with a diagnosis of alcohol dependence [17]. Therefore, prevention and treatment of, especially severe, alcohol use disorders should be considered a public health priority. In order to plan prevention and treatment, information is needed about alcohol use disorders, their course and their risk indicators in the general population. However, current knowledge is strongly skewed because of the emphasis of research on alcohol use disorders in clinical samples, i.e. the subgroup of people who entered treatment and often have very severe alcohol use disorders and serious comorbidity. However, most people with an alcohol use disorder do not enter treatment [18]. Although longitudinal population-based research is costly and complex, it is crucial to increase our understanding of demographic and clinical characteristics of alcohol use disorders in the general population, such as age, sex, chronicity of the disorder, level of impairment, consumption level and comorbid psychopathology. This information is needed to efficiently target prevention and treatment to those cases in greatest need for help.

Notably, the few existing community studies suggest that alcohol use disorders in the general population are generally milder than in clinical samples and that valid notions in clinical samples may not be true in the general population (e.g. an alcohol

use disorder is inherently related to excessive drinking; an alcohol use disorder is a chronic illness; all people with an alcohol use disorder need treatment) [19-22]. Hence, besides identification of those groups in the general population that are more likely to develop alcohol problems, examination of the disorder itself in the general population is crucial. Among others, these studies should investigate the following questions: to which degree are alcohol use disorders related to the level of alcohol intake, what determines whether individuals reach (stable) remission while others do not, and is treatment seeking related to the level of drinking or the severity of the alcohol use disorder? Therefore, this thesis maps the onset, course and treatment of alcohol use disorders in the general population. It examines potential risk indicators of a severe or persistent disorder with specific consideration for possible effects of the level of alcohol intake. These issues are examined using data from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2), a longitudinal population-based study among Dutch adults aged 18-64.

Table 1.1. Definitions of alcohol use disorder according to the two versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM): DSM-IV and DSM-5.

A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress…

DSM-IV: Alcohol Abuse

…as manifested by at least 1 (or more) of the following, occurring within a 12-month period:

1. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
2. Recurrent alcohol use in situations in which it is physically hazardous.
3. Recurrent alcohol-related legal problems.
4. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.

DSM-IV: Alcohol Dependence

…as manifested by 3 (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
   a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
   b. A markedly diminished effect with continued use of the same amount of alcohol.
2. Withdrawal, as manifested by either of the following:
   a. The characteristic withdrawal syndrome for alcohol.
   b. Alcohol is taken to relieve or avoid withdrawal symptoms.
3. Alcohol is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
5. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
7. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.

DSM-5: Alcohol use disorder

…as manifested by at least 2 of the following, occurring at any time in the same 12-month period:

Craving, or a strong desire or urge to use alcohol.
2-11. All abuse and dependence criteria indicated above, except abuse criterion 3 ('legal problems').

Onset of drinking and of alcohol use disorders

Previous research has shown that environmental factors, including parental and school influences [19], play an important role in initiation of alcohol use, but that their effect on the development of problem drinking and the onset of alcohol use disorders is relatively small [20]. However, specific influences, such as childhood psychopathology and traumatic experiences, are important to identify who is at risk of problem drinking or the onset of an alcohol use disorder [20;21]. This thesis specifically focuses on one such influence: the presence of attention-deficit/hyperactivity disorder (ADHD) in childhood. This focus was chosen because previous research suggests that childhood ADHD may be especially useful for timely detection of alcohol-related problems: ADHD generally presents itself at an early age and meta-analyses have shown that ADHD is related to a higher prevalence of alcohol use disorder [27;28]. However, the nature of the link between ADHD and alcohol use disorders is not completely clear and other factors may play an important (confounding) role in this relation [27]. One such factor is conduct disorder (CD): children with ADHD often have a comorbid CD [29], which is also associated with a high risk of alcohol use disorders [30;31]. Previous research showed that children with both ADHD and CD have a higher rate of alcohol use disorders than children with only ADHD [32;33]. The few studies explicitly addressing the role of CD in the association between ADHD and alcohol use (disorder) were inconclusive and pointed to different underlying processes [34-39]. Moreover, most of these studies focused on adolescents or young adults [35-39] and were thus limited to early onset alcohol use disorders. To extend our knowledge into later alcohol use disorders, this thesis examines the role of CD in the relationship of childhood ADHD with alcohol use and alcohol use disorder using retrospective data of a large adult general population sample.

Table 1.2. Alcohol use disorder: DSM-IV vs. DSM-5

The fifth edition of the DSM was released in 2013 [12]. Instead of the two disorders defined in DSM-IV (alcohol abuse [≥ 1 of 4 criteria] and alcohol dependence [≥ 3 of 7 criteria]) [11], DSM-5 has only one alcohol use disorder with three severity levels: mild (2-3 of 11 criteria), moderate (4-5 of 11 criteria), and severe (≥ 6 of 11 criteria) alcohol use disorder. The main reasons for these changes were [59;60]:

- Limited reliability, validity and clinical relevance of alcohol abuse. Alcohol abuse only required presence of one criterion, a diagnosis could thus easily be obtained and was associated with limited stability [61]. DSM-5 removed the diagnosis alcohol abuse and the threshold for an alcohol use disorder diagnosis was set at presence of two criteria.
- Although people with two dependence criteria but no alcohol abuse generally showed more severe pathology than those with a single abuse criterion, they were not diagnosed with an alcohol use disorder in DSM-IV [62;63]. With the new DSM-5 threshold of two or more criteria, these individuals are diagnosed with a mild alcohol use disorder.
- The DSM-IV assumed that abuse preceded the development of alcohol dependence, but research showed otherwise: abuse and dependence criteria are arrayed along a continuum of severity with abuse criteria not always representing the lower level of severity [64]. Therefore, abuse and dependence criteria are combined in DSM-5. Notably, one criterion (legal problems) was removed and another criterion (craving) was added.

Relationship between excessive drinking and alcohol use disorder

The diagnosis of an alcohol use disorder according to psychiatric classification systems such as the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) does not require a minimum level of alcohol consumption [11;12]. It could be argued that excessive drinking is necessary for the development of alcohol-related problems and therefore is an implicit characteristic of the disorder. Although this widespread assumption is supported by the frequently quoted strong link between alcohol use disorders and heavy drinking [8;40;41], findings from the first Netherlands Mental Health Survey and Incidence Study (NEMESIS-1) revealed that this notion is not true for the majority of individuals in the general population with an alcohol use disorder [42]. Only one-third of the individuals with DSM-III-R alcohol abuse and only half of those with alcohol dependence were risky drinkers, defined as drinking more than 14/21 (women/men) drinks per week. In addition, other community studies showed that alcohol-related problems may already occur at relatively low levels of consumption [43;44]. However, the limited overlap between alcohol consumption levels and the presence of alcohol use disorders is not properly understood, partly because these aspects of problematic alcohol use are generally examined separately. Psychiatric surveys mainly report on alcohol use disorder diagnoses without addressing related alcohol consumption levels, whereas public health studies tend to focus on excessive drinking and largely disregard the presence of alcohol use disorders [45].

Simultaneous investigation of excessive drinking and alcohol use disorder is needed to gain more insight in the degree of overlap, and to increase our knowledge about different groups of problematic alcohol users: excessive drinkers without alcohol-related problems, people with alcohol-related problems who do not drink excessively, and people with both characteristics. Moreover, these subgroups may be associated with different patterns of comorbid psychopathology (e.g. mood or anxiety disorders) or functioning. Information regarding such clinical characteristics could thus provide an indication of the clinical relevance of the subgroups. This thesis will therefore address the overlap and differences between excessive drinking and alcohol use disorders by comparing characteristics of excessive drinking only, alcohol use disorder only or both.

Course of alcohol use disorders

Research among patients in addiction treatment suggests that the course of alcohol use disorder is usually chronic and associated with repeated relapses [19]. Information regarding the course of alcohol use disorder in the general population is scarce, mainly because this requires longitudinal population-based research. Yet, the course of alcohol use disorder in the general population has been mapped out by two such studies: NEMESIS-1 and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), conducted in the United States. In contrast with observations in clinical samples, these community studies observed that alcohol use disorders in the general population generally have a favorable course: approximately 60-85% showed

spontaneous (i.e. without formal treatment) diagnostic remission within three years [20;46], with only a small minority of those in remission experiencing relapse [20;21].

Given these high sustained spontaneous remission rates it seems essential to identify risk indicators for the minority with an alcohol use disorder in the general population at risk of a persistent or relapsing course. Specifically, such indicators may improve allocation of care as low intensity interventions could be sufficient for most people while those at risk of a persistent course may need more intensive treatment. Predictors of a chronic course in the general population are available only from the NESARC study, showing that neither sociodemographics nor the presence of psychiatric comorbidity were strongly associated with the persistence of an alcohol use disorder. However, a higher number of alcohol use disorder criteria (i.e. severity) did predict both a persistent course [22] and relapse [21]. Persistence was also associated with a higher level of alcohol consumption [22], but the role of consumption was not examined with respect to relapse. This thesis extends the previous observations in two important ways. First, it aims to replicate the findings of NESARC regarding the persistence of alcohol use disorders in order to verify the validity of these findings for the Netherlands. Second, it aims to study the role of the level of alcohol consumption on relapse after diagnostic remission. This is important, because diagnostic remission from an alcohol use disorder is not the same as abstinence from alcohol use since continued high levels of drinking may occur during remission. This would not only suggest that high remission rates should be interpreted with caution, it may in fact mark an increased risk of relapse of an alcohol use disorder.

Treatment seeking for alcohol use disorders

A robust worldwide finding of previous research has been that the number of individuals with an alcohol use disorder greatly exceeds the number of people in treatment [47]. This is also true for the Netherlands. According to NEMESIS-2, approximately 478,000 adults aged 18-64 were affected by an alcohol use disorder in The Netherlands in the period 2007 to 2009 [14]. However, according to the Dutch national alcohol and drugs information system (LADIS), only a little over 30,000 people (i.e. 6.5% of those with an alcohol use disorder) entered addiction treatment because of alcohol problems in 2008 [48]. This very low rate of addiction treatment for people with an alcohol use disorder has been stable for the past five years [48].

Concerns about this treatment gap have been raised for decades [49-51], and several solutions have been proposed [52]. However, the magnitude of the treatment gap can be questioned given the high spontaneous remission rate of alcohol use disorders in the general population [20;22]. It is undesirable when severe cases do not receive treatment, but when non-treatment users turn out to be mild cases with a favorable course, their decision not to seek treatment may be justified and cost-effective. It is therefore important to understand to what extend severe clinical characteristics of alcohol use disorder are associated with treatment seeking. This has not been examined in the Netherlands so far, but a study in the United States found that illness severity in terms

of number of criteria and impairment played a role in the decision to seek treatment [18]. However, the level of consumption was not taken into account in that study. Particular attention should be paid to the potential unmet need for treatment of two distinct groups. First, people who do not seek treatment specifically for their alcohol problems but who do seek treatment for their comorbid mental health problems. When needed, these individuals can for example be guided to additional alcohol treatment via attention to dual diagnosis [53]. Second, people who neither seek treatment for mental health nor for alcohol problems. This group is more difficult to reach but possibly their unmet need for treatment could be signaled when they make a primary care visit for physical problems related to their excessive drinking [54].

METHOD

In this thesis, the onset, course and treatment of people with an alcohol use disorder in the general population are examined using data from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2). NEMESIS-2 is an ongoing prospective cohort study examining the prevalence, incidence, course and consequences of mental disorders - including alcohol use disorders - in the general Dutch adult population. For the present thesis, data from the first two waves were available.

NEMESIS-2 is based on a multistage, stratified, random sampling of households, with one respondent randomly selected in each household. In the first wave (T_0), performed from November 2007 to July 2009, a total of 6,646 persons aged 18-64 were interviewed (response: 65.1%). The average interview duration was 95 minutes. This sample was nationally representative, although younger subjects were somewhat underrepresented [55]. All T_0 respondents were approached for follow-up (T_1), three years after T_0 from November 2010 to June 2012. Of this group, a total of 5,303 persons were interviewed again (response: 80.4%, with those deceased excluded). The average interview duration at the second wave was 84 minutes and the mean period between the two interviews was 3 years and 7 days. Attrition was not significantly linked to any of 12-month mental disorders at baseline, after controlling for sociodemographic variables such as age and sex [56]. Note that this was also true for the mental disorders under study here, alcohol use disorders.

Both waves consisted of a face-to-face interview, mostly held at the respondents' home. The assessment included detailed information on sociodemographics, mental and physical functioning, service utilization, and mental disorders (i.e. externalizing childhood disorders, mood disorders, anxiety disorders, and substance use disorders). More specific, mental disorders according to the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV [11]) were assessed using the third version of the Composite International Diagnostic Interview (CIDI 3.0) [57]. Clinical calibration studies conducted in various countries have found that the CIDI 3.0 assesses anxiety, mood and substance use disorders with generally good validity

compared to blinded clinical reappraisal interviews [58]. Besides the diagnosis of alcohol use disorders, the alcohol section of the CIDI 3.0 also assesses: onset and recency of the disorder; age of first alcohol use and age of first regular use; quantity and frequency of alcohol use in the past 12 months and in a person's most severe drinking period; the degree of alcohol-related functional impairment; and treatment contact for alcohol problems. In NEMESIS-2, a lifetime CIDI version was used at T_0; a CIDI version with the period between T_0 and T_1 as timeframe was used at T_1. Both at T_0 and T_1, also the presence of 12-month mental disorders was assessed.

AIMS AND OUTLINE OF THIS THESIS

The main objective of this thesis is to enhance our understanding of the onset, course and treatment of alcohol use disorder in the general population, with special emphasis on the role of ADHD and CD in the onset of alcohol use disorders and the level of alcohol consumption in remission and relapse. The core aspects of the thesis are described below. Notably, the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM), introducing a single alcohol use disorder, appeared in the period that NEMESIS-2 was conducted and the chapters of this thesis were written [12]. To provide up-to-date findings, the chapters that were written after the DSM-5 release (**chapter 3** to **chapter 6**) focused on the DSM-5 alcohol use disorder.

- **Chapter 2** retrospectively examines the relationship of childhood ADHD and CD with (age of) onset of three stages of alcohol use measured at T_0: alcohol initiation, regular drinking (defined as ≥ 12 drinks per year), and DSM-IV alcohol use disorder.
- **Chapter 3** examines the cross-sectional overlap between excessive alcohol consumption and both DSM-IV and DSM-5 alcohol use disorder at T_0. Three subgroups of problematic drinkers (excessive drinking only, alcohol use disorder only, excessive drinking and alcohol use disorder) are compared with non-problematic drinkers on demographics, psychiatric comorbidity, functioning and treatment utilization.
- **Chapter 4** investigates 3-year persistence rates and predictors of a persistent course of DSM-5 alcohol use disorders. Special attention is paid to the level of alcohol consumption in those achieving diagnostic remission.
- **Chapter 5** examines relapse at T_1 among those people with a lifetime but not a past-year DSM-5 alcohol use disorder at T_0. Also, predictors of relapse were examined with special emphasis on the number of lifetime alcohol use disorder criteria and the level of alcohol consumption.
- **Chapter 6** examines the 4-year treatment gap for DSM-5 alcohol use disorders. The process of treatment seeking is addressed by an examination of determinants of treatment seeking as well as by an investigation of how those without specialized alcohol treatment are functioning at follow-up.
- **Chapter 7** summarizes and discusses the main findings of the studies included in this thesis.

REFERENCES

1. World Health Organization. *Global status report on alcohol and health*. Geneva: World Health Organization (WHO); 2014.
2. Statistics Netherlands. *www.statline.cbs.nl*. Den Haag: Statistics Netherlands (CBS); 2015.
3. Gordon R., Heim D., MacAskill S. Rethinking drinking cultures: a review of drinking cultures and a reconstructed dimensional approach. *Public Health* 2012; **126**: 3-11.
4. Crutzen R., Kuntsche E. Validation of the four-dimensional structure of drinking motives among adults. *Eur Addict Res* 2013; **19**: 222-6.
5. van Amsterdam J., Opperhuizen A., Koeter M., van den Brink W. Ranking the harm of alcohol, tobacco and illicit drugs for the individual and the population. *Eur Addict Res* 2010; **16**: 202-7.
6. van Amsterdam J., van den Brink W. The high harm score of alcohol. Time for drug policy to be revisited? *J Psychopharmacol* 2013; **27**: 248-55.
7. Nutt D., King L.A., Saulsbury W., Blakemore C. Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* 2007; **369**: 1047-53.
8. Schuckit M.A. Alcohol-use disorders. *Lancet* 2009; **373**: 492-501.
9. Hasin D.S., Stinson F.S., Ogburn E., Grant B.F. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2007; **64**: 830-42.
10. Rehm J., Dawson D., Frick U., Gmel G., Roerecke M., Shield K.D. *et al.* Burden of disease associated with alcohol use disorders in the United States. *Alcohol Clin Exp Res* 2014; **38**: 1068-77.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. Washington, DC: American Psychiatric Association (APA); 1994.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Washington, DC: American Psychiatric Association (APA); 2013.
13. World Health Organization. *Global status report: Alcohol policy*. Geneva: World Health Organization (WHO); 2004.
14. de Graaf R., ten Have M., van Dorsselaer S. *De psychische gezondheid van de Nederlandse bevolking. NEMESIS-2: opzet en resultaten*. Utrecht: Trimbos instituut; 2010.
15. Rehm J., Mathers C., Popova S., Thavorncharoensap M., Teerawattananon Y., Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; **373**: 2223-33.
16. Rehm J., Shield K.D., Rehm M.X., Gmel G., Frink U. *Alcohol consumption, alcohol dependence and attributable burden of disease in Europe. Potential gains from effective interventions for alcohol dependence*. Toronto, ON: Centre for Addiction and Mental Health; 2012.
17. Rehm J., Shield K.D., Gmel G., Rehm M.X., Frick U. Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *Eur Neuropsychopharmacol* 2013; **23**: 89-97.
18. Edlund M.J., Booth B.M., Han X. Who seeks care where? Utilization of mental health and substance use disorder treatment in two national samples of individuals with alcohol use disorders. *J Stud Alcohol Drugs* 2012; **73**: 635-46.
19. Cunningham J.A., McCambridge J. Is alcohol dependence best viewed as a chronic relapsing disorder? *Addiction* 2012; **107**: 6-12.
20. de Bruijn C., van den Brink W., de Graaf R., Vollebergh W. The three year course of alcohol use disorders in the general population: DSM-IV, ICD-10 and the

Craving Withdrawal Model. *Addiction* 2006; **101**: 385-92.

21. Dawson D.A., Goldstein R.B., Grant B.F. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: A 3-year follow-up. *Alcohol Clin Exp Res* 2007; **31**: 2036-45.
22. Dawson D.A., Goldstein R.B., Ruan W.J., Grant B.F. Correlates of recovery from alcohol dependence: A prospective study over a 3-year follow-up interval. *Alcohol Clin Exp Res* 2012; **36**: 1268-77.
23. Lipperman-Kreda S., Grube J.W., Paschall M.J. Community norms, enforcement of minimum legal drinking age laws, personal beliefs and underage drinking: an explanatory model. *J Community Health* 2010; **35**: 249-57.
24. Kendler K.S., Schmitt E., Aggen S.H., Prescott C.A. Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. *Arch Gen Psychiatry* 2008; **65**: 674-82.
25. Rhee S.H., Hewitt J.K., Young S.E., Corley R.P., Crowley T.J., Stallings M.C. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Arch Gen Psychiatry* 2003; **60**: 1256-64.
26. Derks E.M., Vink J.M., Willemsen G., van den Brink W., Boomsma D.I. Genetic and environmental influences on the relationship between adult ADHD symptoms and self-reported problem drinking in 6024 Dutch twins. *Psychol Med* 2014; **44**: 2673-83.
27. Lee S.S., Humphreys K.L., Flory K., Liu R., Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: A meta-analytic review. *Clinical Psychology Review* 2011; **31**: 328-41.
28. Charach A., Yeung E., Climans T., Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: Comparative meta analyses. *J Am Acad Child Adolesc Psychiatry* 2011; **50**: 9-21.
29. Langley K., Fowler T., Ford T., Thapar A.K., van den Bree M., Harold G. *et al.* Adolescent clinical outcomes for young people with attention-deficit hyperactivity disorder. *Br J Psychiatry* 2010; **196**: 235-40.
30. Nock M.K., Kazdin A.E., Hiripi E., Kessler R.C. Prevalence, subtypes, and correlates of DSM-IV conduct disorder in the National Comorbidity Survey Replication. *Psychol Med* 2006; **36**: 699-710.
31. Glantz M.D., Anthony J.C., Berglund P.A., Degenhardt L., Dierker L., Kalaydjian A. *et al.* Mental disorders as risk factors for later substance dependence: Estimates of optimal prevention and treatment benefits. *Psychol Med* 2009; **39**: 1365-77.
32. Biederman J., Mick E., Faraone S.V., Burback M. Patterns of remission and symptom decline in conduct disorder: A four-year prospective study of an ADHD sample. *J Am Acad Child Adolesc Psychiatry* 2001; **40**: 290-8.
33. Molina B.S.G., Pelham W.E., Gnagy E.M., Thompson A.L., Marshal M.P. Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. *Alcohol Clin Exp Res* 2007; **31**: 643-54.
34. Knop J., Penick E.C., Nickel E.J., Mortensen E.L., Sullivan M.A., Murtaza S. *et al.* Childhood ADHD and conduct disorder as independent predictors of male alcohol dependence at age 40. *J Stud Alcohol Drugs* 2009; **70**: 169-77.
35. Kuperman S., Schlosser S.S., Kramer J.R., Bucholz K., Hesselbrock V., Reich T. *et al.* Developmental sequence from disruptive behavior diagnosis to adolescent alcohol dependence. *Am J Psychiatry* 2001; **158**: 2022-6.
36. Disney E.R., Elkins I.J., McGue M., Iacono W.G. Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. *Am J Psychiatry* 1999; **156**: 1515-21.
37. Molina B.S.G., Bukstein O.G., Lynch K.G. Attention-deficit/hyperactivity disorder and conduct disorder symptomatology

in adolescents with alcohol use disorder. *Psychol Addict Behav* 2002; **16**: 161-4.

38. Flory K., Milich R., Lynam D.R., Leukefeld C., Clayton R. Relation between childhood disruptive behavior disorders and substance use and dependence symptoms in young adulthood: individuals with symptoms of attention-deficit/hyperactivity disorder and conduct disorder are uniquely at risk. *Psychol Addict Behav* 2003; **17**: 151-8.
39. Fergusson D.M., Horwood L.J., Ridder E.M. Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: Results of a 25-year longitudinal study. *Drug Alcohol Depend* 2007; **88**: S14-S26.
40. Rubinsky A.D., Dawson D.A., Williams E.C., Kivlahan D.R., Bradley K.A. AUDIT-C scores as a scaled marker of mean daily drinking, alcohol use disorder severity, and probability of alcohol dependence in a U.S. general population sample of drinkers. *Alcohol Clin Exp Res* 2013; **37**: 1380-90.
41. Dawson D.A., Li T.K., Grant B.F. A prospective study of risk drinking: at risk for what? *Drug Alcohol Depend* 2008; **95**: 62-72.
42. Verdurmen J., Monshouwer K., van Dorsselaer S., de Graaf R. *Bovenmatig drinken in Nederland (Excessive drinking in the Netherlands)*. Utrecht: Trimbos-instituut; 2003.
43. Caetano R., Mills B., Pinsky I., Zaleski M., Laranjeira R. The distribution of alcohol consumption and the prevention paradox in Brazil. *Addiction* 2012; **107**: 60-8.
44. Gmel G., McKeganey N., Klingemann S., Müller R., Brenner D. Revising the preventive paradox: The Swiss case. *Addiction* 2001; **96**: 273-84.
45. Rehm J., Baliunas D., Borges G.L.G., Graham K., Irving H., Kehoe T. *et al.* The relation between different dimensions of alcohol consumption and burden of disease: An overview. *Addiction* 2010; **105**: 817-43.
46. Dawson D.A., Li T.K., Chou S.P., Grant B.F. Transitions in and out of alcohol use disorders: their associations with conditional changes in quality of life over a 3-year follow-up interval. *Alcohol Alcohol* 2009; **44**: 84-92.
47. Rehm J., Greenfield T.K. Public alcohol policy: current directions and new opportunities. *Clin Pharmacol Ther* 2008; **83**: 640-3.
48. Wisselink D.J., Kuijpers W.G.T., Mol A. *Kerncijfers verslavingszorg 2013: Landelijk Alcohol en Drugs Informatie Systeem (LADIS).* Houten: Informatievoorziening zorg (IVZ); 2014.
49. Kohn R., Saxena S., Levav I., Saraceno B. The treatment gap in mental health care. *Bull World Health Organ* 2004; **82**: 858-66.
50. Cohen E., Feinn R., Arias A., Kranzler H.R. Alcohol treatment utilization: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Depend* 2007; **86**: 214-21.
51. Grella C.E., Karno M.P., Warda U.S., Moore A.A., Niv N. Perceptions of need and help received for substance dependence in a national probability survey. *Psychiatr Serv* 2009; **60**: 1068-74.
52. van Amsterdam J., van den Brink W. Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. *J Psychopharmacol* 2013.
53. Swendsen J., Conway K.P., Degenhardt L., Glantz M., Jin R., Merikangas K.R. *et al.* Mental disorders as risk factors for substance use, abuse and dependence: results from the 10-year follow-up of the National Comorbidity Survey. *Addiction* 2010; **105**: 1117-28.
54. Li T.K., Hewitt B.G., Grant B.F. Is there a future for quantifying drinking in the diagnosis, treatment, and prevention of alcohol use disorders? *Alcohol Alcohol* 2007; **42**: 57-63.
55. de Graaf R., ten Have M., van Dorsselaer S. The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. *Int J Methods Psychiatr Res* 2010; **19**: 125-41.
56. de Graaf R., van Dorsselaer S., Tuithof M., ten Have M. Sociodemographic and

psychiatric predictors of attrition in the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). *Compr Psychiatry* 2013; **54**: 1131-9.

57. Kessler R.C., Ustun T.B. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res* 2004; **13**: 93-121.
58. Haro J.M., Arbabzadeh-Bouchez S., Brugha T.S., de Girolamo G., Guyer M.E., Jin R. *et al.* Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. *Int J Methods Psychiatr Res* 2006; **15**: 167-80.
59. Agrawal A., Heath A.C., Lynskey M.T. DSM-IV to DSM-5: The impact of proposed revisions on diagnosis of alcohol use disorders. *Addiction* 2011; **106**: 1935-43.
60. Hasin D.S., O'Brien C.P., Auriacombe M., Borges G., Bucholz K., Budney A. *et al.* DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry* 2013; **170**: 834-51.
61. Hasin D., Van Rossem R., McCloud S., Endicott J. Alcohol dependence and abuse diagnoses: Validity in community sample heavy drinkers *Alcohol Clin Exp Res* 1997; **21**: 213-9.
62. Harford T.C., Yi H.Y., Grant B.F. The five-year diagnostic utility of 'diagnostic orphans' for alcohol use disorders in a national sample of young adults. *J Stud Alcohol Drugs* 2010; **71**: 410-7.
63. Hasin D., Paykin A. Dependence symptoms but no diagnosis: Diagnostic 'orphans' in a community sample. *Drug Alcohol Depend* 1998; **50**: 19-26.
64. Keyes K.M., Krueger R.F., Grant B.F., Hasin D.S. Alcohol craving and the dimensionality of alcohol disorders. *Psychol Med* 2011; **41**: 629-40.

Chapter 2

The role of conduct disorder in the association between ADHD and alcohol use (disorder)

Results from the Netherlands Mental Health Survey and Incidence Study-2

ABSTRACT

Background

Much is unclear about the association between attention-deficit/hyperactivity disorder (ADHD) and alcohol use (disorder). Research on this subject is hindered by the role of conduct disorder (CD). We investigate whether (i) childhood ADHD is associated with higher prevalence and earlier onset of alcohol initiation, regular alcohol use and alcohol use disorder (AUD); (ii) CD mediates or modifies this association.

Methods

Data were derived from the baseline assessment of the Netherlands Mental Health Survey and Incidence Study-2, a general population study. ADHD and CD were assessed among respondents aged 18-44 (n = 3,309). ADHD, CD, and alcohol use (disorder) were assessed using the Composite International Diagnostic Interview 3.0.

Results

Lifetime prevalence was 2.9% for ADHD, 5.6% for CD, 94.3% for alcohol initiation, 85.7% for regular alcohol use and 19.0% for AUD; mean ages of onset were 6.7, 11.5, 14.8, 16.7 and 19.2 years, respectively. After correction for gender and age, ADHD was associated with a higher prevalence of all three stages of alcohol use, but not with earlier onset of these stages. The association between ADHD and prevalence of AUD was fully explained by a mediating role of CD. CD did not modify the associations between ADHD and prevalence and onset of alcohol use (disorder).

Conclusions

The mediating role of CD in the association between ADHD and AUD suggests a developmental pathway from ADHD to CD and subsequent AUD. Early interventions in children with ADHD may prevent CD and subsequent onset of AUD.

Marlous Tuithof, Margreet ten Have, Wim van den Brink, Wilma Vollebergh, Ron de Graaf

Published in Drug and Alcohol Dependence (2012) 123: 115-121.

INTRODUCTION

Clinical and epidemiological studies indicate that childhood attention-deficit/hyperactivity disorder (ADHD) is associated with a higher prevalence [1-7] and an earlier onset [6-9] of alcohol use and of alcohol use disorder (AUD). However, results have been inconsistent, especially with regard to the prevalence of alcohol use [2;5;10-12]. Recent meta-analyses on this matter suggest a significant effect of ADHD on the prevalence of AUD [10;13], but not on alcohol use [10]. Lee et al. [10] concluded, however, that the results on which they based their conclusions were somewhat heterogeneous, indicating that other factors might play a role in the association between ADHD and alcohol use (disorder). This is further demonstrated by the finding that conduct disorder (CD) is highly associated with both ADHD [14-16] and alcohol use (disorder) [4;17]. Children with ADHD as well as CD have a higher rate of AUD compared to children with ADHD only [18;19]; thus CD possibly confounds the assumed association between ADHD and AUD. Many studies, however, failed to examine explicitly the role of CD in this association [2-10].

Studies that tried to identify the association between ADHD, CD, and alcohol use (disorder) [1;12;20-23] can be divided into two approaches. The first approach suggests a developmental sequence with ADHD influencing the development of CD, which in turn results in a higher risk of alcohol use (disorder) [20]. This so-called mediating role of CD has been found in prospective studies focusing on the role of CD in the association between ADHD and substance use disorder [15;23-25]. Most of these studies focused on substance use disorder in general, only one [23] explicitly addressed alcohol use (disorder) in young adulthood. Unfortunately, this study measured attention and conduct problems and did not define ADHD and CD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) [26]. Thus, it is still not clear whether there actually is a mediating role of CD in the association between ADHD and alcohol use (disorder). The second approach suggests that children with both ADHD and CD represent a distinct subgroup which has an additionally increased risk of alcohol use (disorder) compared to children with ADHD only or CD only. However, studies on this modifying role of CD have shown conflicting results [1;12;21;22]. Specifically, only one study supported the idea that children with both ADHD and CD have an additionally increased risk of AUD [1]. Other studies [12;21;22] found that children with both ADHD and CD had a higher prevalence of alcohol use (disorder) compared to children with ADHD only or CD only, but the risk of alcohol use (disorder) was not additionally increased in this group of children. Differences in sampling design could play a role in these mixed findings. Knop et al. [1] focused on adults, others on adolescents [12;21] or young adults [22]. The differential results could imply that the modifying role of CD begins to express itself in adulthood. However, further examination of this hypothesis is needed. Thus, research on both approaches with respect to the role of CD in the association between ADHD and prevalence of alcohol use (disorder) has

been inconclusive. To our knowledge, research on both approaches with respect to the age of onset of alcohol use (disorder) is lacking.

Whether CD plays a mediating or modifying role is of great importance for clinical practice. A mediating role would imply that early interventions among children with ADHD are needed to prevent progress from ADHD into CD and subsequent alcohol use (disorder) whereas a modifying role would suggest early diagnosis and intensive treatment of those at highest risk of alcohol use (disorder), being children with both ADHD and CD.

Using data from the baseline assessment of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), we will address two questions in particular: (i) whether childhood ADHD is associated with a higher lifetime prevalence and an earlier onset of three stages of alcohol use: alcohol initiation, regular alcohol use, and AUD; and (ii) whether CD mediates or modifies this association. The present study will increase the existing knowledge in four ways. First, to our knowledge, this study is the first to examine the association between ADHD and both prevalence and age of onset of three different stages of alcohol use. Second, both the mediating and modifying role of CD in the association between ADHD and alcohol use (disorder) will be examined. Third, using data of a general population study enables us to examine associations which are applicable to the population at large. Moreover, the use of an adult sample enables us to associate childhood ADHD with AUD at a much later age than most other studies in which the association between ADHD, CD, and alcohol use (disorder) was examined [12;21-23]. This provides us the opportunity to study processes that emerge in adulthood. Fourth, not symptom counts but DSM-IV diagnoses of ADHD, CD, and AUD will be used.

METHODS

Sample and assessment procedures

Data were derived from the baseline assessment of NEMESIS-2. Methods have been reported elsewhere [27]. Briefly, NEMESIS-2 is based on a multistage, stratified, random sampling of households, with one respondent randomly selected in each household (response: 65.1%). The Composite International Diagnostic Interview (CIDI) version 3.0 was used to determine the presence of ADHD, CD, and AUD according to DSM-IV criteria. The CIDI is a fully structured, lay administered interview developed by the World Health Organization. The CIDI is used worldwide, and has been shown to be a reliable and valid instrument [28]. To increase accuracy of retrospective recall, ADHD and CD were only assessed among respondents aged 18-44, conform [29]. This resulted in a total sample of 3,309 respondents.

ADHD and CD. Respondents who answered positively to one of the screener questions for ADHD or for CD entered the relevant CIDI sections. In these sections symptoms

of the disorder, impairment due to these symptoms, and age of onset were assessed. Computerized CIDI algorithms were used to generate diagnoses according to full DSM-IV criteria.

Alcohol use (disorder). All participants entered the alcohol section which started with a question to measure alcohol initiation: "How old were you the very first time you ever drank an alcoholic beverage?". Only participants who reported ever-use continued with the alcohol section, the next question assessed regular drinking: "How old were you when you first started drinking at least 12 drinks per year?". Only participants who reported regular drinking continued with the next part of the alcohol module assessing symptoms of alcohol abuse and dependence, impairment due to these symptoms, and age of onset.

Analyses

Analyses were performed using Stata version 11.1 which enabled us to control for the complex sampling and recruitment procedure of the study. We first established unweighted counts, and then calculated weighted prevalence rates and weighted means to provide characteristics of the sample and summary statistics of ADHD, CD, and alcohol use (disorder). The data were weighted to ensure they were representative of the national population.

The association between ADHD, CD, and prevalence of alcohol use (disorder). Cox regression analyses, which generate hazard ratios (HR), were conducted to test whether ADHD was associated with a higher prevalence rate of alcohol use (disorder) in a univariable model. Cox regression takes both the age of the respondents and the age of onset of alcohol use (disorder) into account. Before conducting these analyses, the proportional hazards assumption was checked; the assumption was not violated in the univariable models.

Next, stepwise Cox regression analyses were conducted. These analyses were adjusted for gender to account for the higher prevalence rates of ADHD and alcohol use (disorder) in males [30;31]. In analyses with alcohol initiation and regular alcohol use, gender was stratified to suffice the proportional hazards assumption [32], stratification was not needed in analyses with AUD. In the first step, we examined whether ADHD was associated with all stages of alcohol use. In the second step, we added CD as a covariate to these models in order to investigate its mediating role. The Sobel test was used to test for significance of mediation [33] after correction for the dichotomous nature of the mediator and outcome variable [34].

In the third step it was investigated whether CD modified the association between ADHD and alcohol use (disorder) using an additive model. Additive interaction exists if the combined effect of ADHD and CD on alcohol use (disorder) is stronger than the sum of the separate effects. Additive interaction was tested by comparing the HR of ADHD and CD combined with the expected value in case of no interaction, namely

HR (AB) ≈ HR (A) + HR (B) - 1. If the expected HR is smaller than the lower boundary of the 95% confidence interval of the HR of the combined effect, additive interaction is assumed [35;36].

The association between ADHD, CD, and age of onset of alcohol use (disorder). We conducted linear regression analyses, which generate unstandardized coefficients (Bs), to determine whether ADHD was associated with an earlier age of onset of alcohol use in a univariable model. Next, stepwise linear regression analyses, adjusted for age and gender, were used to test the association between ADHD, CD, and onset of alcohol use (disorder). In the first step, we examined whether ADHD was still associated with the onset of alcohol use. In the second step, we added CD to the model in order to test whether CD mediated this association. Again, significance of mediation was checked with the Sobel test. The interaction-term of ADHD and CD was included in the third step in order to examine whether CD modified the association between ADHD and onset of alcohol use (disorder) in an additive model. Level of significance was set at 0.05.

RESULTS

Table 2.1 provides characteristics of the sample and summary statistics of ADHD, CD, and alcohol use (disorder) as unweighted counts, weighted percentages and weighted means. Mean age of the 3,309 respondents was 32.0 and 50.4% was male.

Childhood ADHD was present in 2.9% (n = 74) of the respondents. Respondents with ADHD were significantly younger than respondents without ADHD (28.9 vs. 32.1; $t(3,307) = -2.81$; $p = 0.01$) and they were more often male (74.8% vs. 49.6%; OR = 3.0; $p < 0.001$). CD was present in 5.6% (n = 127) of the respondents. As expected, childhood CD was much more prevalent in respondents with ADHD than in respondents without ADHD (40.0% vs. 4.5%; OR = 14.0; $p < 0.001$). Mean age of onset of ADHD was substantially lower than that of CD (6.7 vs. 11.5). More specific, 83.7% of the respondents fulfilling criteria for both disorders reported that symptoms of ADHD were present before or at the same time as symptoms of CD.

Most respondents initiated alcohol use (94.3%; mean age 14.8) and regular alcohol use (85.7%; mean age 16.7). Alcohol abuse and dependence were prevalent in respectively 16.6% (n = 472) and 2.4% (n = 54) of respondents. Given the small number of respondents with alcohol dependence, both diagnoses were combined (AUD; 19.0%, n = 526; mean age of onset 19.2) in the analyses. Symptoms of ADHD were present before or at the same time as alcohol initiation, regular alcohol use, and AUD in respectively 93.1%, 95.4%, and 100.0% of the respondents with both ADHD and the corresponding stage of alcohol use. Symptoms of CD were somewhat less present before or at the same time as the three stages of alcohol use, namely in 75.4%, 89.3.%, and 94.7% of the respondents with both CD and the corresponding stage of alcohol use.

Table 2.1. Characteristics of the total sample and of respondents with or without attention-deficit/hyperactivity disorder (ADHD). Lifetime prevalence and mean ages of onset (AOO) of ADHD, conduct disorder (CD), and alcohol use (disorder). Results of summary statistics in unweighted counts, weighted column percentages, and weighted means with 95% confidence intervals (95% CI).

	Total sample				Respondents with ADHD				Respondents without ADHD			
Sample characteristics	**n**	**%**	**Mean age**	**(95% CI)**	**n**	**%**	**Mean age**	**(95% CI)**	**n**	**%**	**Mean age**	**(95% CI)**
Total	3,309	100.0	32.0	(31.6; 32.4)	74	100.0	28.9	(26.6; 31.2)	3,235	100.0	32.1	(31.7; 32.5)
Males	1,450	50.4	32.1	(31.6; 32.6)	42	74.8	28.1	(25.0; 31.2)	1,408	49.6	32.3	(31.9; 32.7)
Females	1,859	49.6	31.9	(31.4; 32.5)	32	25.2	31.3	(28.7; 33.9)	1,827	50.4	31.9	(31.4; 32.5)

	Total sample				Respondents with ADHD				Respondents without ADHD			
Sample characteristics	**n**	**%**	**Mean AOO**	**(95% CI)**	**n**	**%**	**Mean AOO**	**(95% CI)**	**n**	**%**	**Mean AOO**	**(95% CI)**
ADHD	74	2.9	6.7	(5.4; 8.0)	74	100.0	6.7	(5.4; 8.0)	-	-	-	-
CD	127	5.6	11.5	(10.6; 12.4)	21	40.0	10.8	(9.3; 12.4)	106	4.5	11.7	(10.7; 12.7)
Alcohol initiation	3,143	94.3	14.8	(14.7; 14.9)	74	100.0	13.8	(12.8; 14.7)	3,069	94.1	14.8	(14.7; 15.0)
Regular alcohol use	2,846	85.7	16.7	(16.5; 16.8)	66	95.2	15.6	(14.9; 16.3)	2,780	85.4	16.7	(16.5; 16.9)
Alcohol use disorder	526	19.0	19.2	(18.7; 19.7)	24	42.7	19.9	(17.3; 22.5)	502	18.2	19.1	(18.7; 19.6)
Alcohol abuse	472	16.6	19.3	(18.8; 19.8)	20	35.4	19.9	(16.9; 22.8)	452	16.0	19.3	(18.7; 19.8)
Alcohol dependence	54	2.4	19.6	(18.1; 21.2)	4	7.3	19.9	(9.9; 29.8)	50	2.3	19.6	(18.2; 21.0)

The association between ADHD, CD, and prevalence of alcohol use (disorder)

All stages of alcohol use were significantly more prevalent in respondents with ADHD than in respondents without ADHD (Table 2.1). The results of the univariable Cox regression analyses (Table 2.2) support this observation: ADHD was associated with a 54% higher risk of alcohol initiation and a 59% higher risk of regular alcohol use. ADHD almost tripled the risk of developing AUD. Step 1 of Table 2.2 shows that these risks slightly decreased, but remained significant, when gender was added to the model.

After adjustment for CD, respondents with ADHD were still more likely to initiate alcohol use ($p = 0.05$) and to start regular drinking ($p = 0.03$). However, ADHD and AUD were no longer significantly associated after adjustment for CD ($p = 0.33$), indicating a mediating role of CD.

To further investigate whether the association between ADHD and one of the stages of alcohol use operates also via CD as the mediating variable, we compared the HRs of ADHD in Step 1 and Step 2 of Table 2.2. The HR for alcohol initiation slightly declined from 1.42 (Step 1) to 1.37 (Step 2) when CD was added to the model (a non-significant reduction of 3.6%, ((1.42 / 1.37) - 1) * 100; Sobel test: $Z = 0.80$; $p = 0.42$). The HR for regular alcohol use declined from 1.42 (Step 1) to 1.34 (Step 2) (a non-significant reduction of 6.0%, ((1.42 / 1.34) - 1) * 100; Sobel test: $Z = 1.13$; $p = 0.26$). Thus, the association between ADHD and alcohol initiation as well as the association between ADHD and regular alcohol use were not significantly mediated by CD. However, the HR for AUD sharply declined from 2.29 (Step 1) to 1.39 (Step 2) (a significant reduction of 64.7%, ((2.29 / 1.39) - 1) * 100; Sobel test: $Z = 4.93$; $p < 0.001$), indicating that ADHD affected the prevalence of AUD via mediation by CD. Additional analyses demonstrated that this conclusion holds after exclusion of those individuals with CD predating ADHD (16.3%).

The final part of Table 2.2 indicates that CD did not modify the association between ADHD and presence of alcohol use (disorder). This is shown by the fact that the combined effect of ADHD and CD on alcohol use (disorder) is not stronger than the sum of the separate effects.

The association between ADHD, CD, and age of onset of alcohol use (disorder)

Respondents with ADHD had an earlier age of onset of alcohol initiation and regular alcohol use than respondents without ADHD (Table 2.1). The univariable linear regression analyses also show that ADHD was associated with an earlier onset of alcohol initiation and regular alcohol use, but not of AUD (Table 2.3). When age and gender were added to the model the differences in onset disappeared (Step 1). Further analyses demonstrated neither a mediating (Step 2) nor a modifying (Step 3) role of CD in the association between ADHD and onset of alcohol use (disorder). However, CD was significantly associated with an earlier onset of AUD.

Table 2.2. The mediating and modifying role of conduct disorder (CD) in the association between attention-deficit/hyperactivity disorder (ADHD) and the prevalence of different stages of alcohol use. Results of Cox regression analyses generating hazard ratios (HR) and adjusted hazard ratios (adj. HR), with 95% confidence intervals (95% CI).

Univariable model	Alcohol initiation			Regular alcohol use			Alcohol use disorder		
	HR	(95% CI)	p	HR	(95% CI)	p	HR	(95% CI)	p
ADHD	1.54	(1.15; 2.05)	0.004	1.59	(1.26; 2.00)	< 0.001	2.90	(1.76; 4.77)	< 0.001

Multivariable model	Alcohol initiation			Regular alcohol use			Alcohol use disorder		
	Adj. HR	(95% CI) [a]	p	Adj. HR	(95% CI) [a]	p	Adj. HR	(95% CI) [b]	p
Step 1									
ADHD	1.42	(1.05; 1.92)	0.02	1.42	(1.12; 1.79)	0.004	2.29	(1.37; 3.81)	0.002
Step 2									
ADHD	1.37	(1.00; 1.87)	0.05	1.34	(1.04; 1.74)	0.03	1.39	(0.72; 2.69)	0.33
CD	1.12	(0.85; 1.46)	0.42	1.16	(0.90; 1.51)	0.25	3.40	(2.33; 4.96)	< 0.001

Combined effect of		Alcohol initiation				Regular alcohol use				Alcohol use disorder			
ADHD	CD	Adj. HR	(95% CI) [a]	p	Expected HR [c]	Adj. HR	(95% CI) [a]	p	Expected HR [c]	Adj. HR	(95% CI) [b]	p	Expected HR [c]
No	No	1.00	-	-		1.00	-	-		1.00	-	-	
Yes	No	1.40	(0.97; 2.02)	0.08		1.36	(0.98; 1.90)	0.07		2.34	(1.29; 4.24)	0.005	
No	Yes	1.13	(0.82; 1.55)	0.45		1.17	(0.86; 1.60)	0.32		3.96	(2.80; 5.60)	< 0.001	
Yes	Yes	1.47	(0.91; 2.38)	0.11	1.53	1.53	(1.12; 2.09)	0.008	1.53	3.02	(1.15; 7.89)	0.03	5.30

[a] Analyses were stratified by gender.
[b] Analyses were controlled for gender.
[c] Expected HR in the case of no interaction is the sum of the separate effects of ADHD and CD. Additive interaction is assumed if the expected HR lays below the lower limits of the confidence intervals of the combined effect of ADHD and CD.

Table 2.3. The mediating and modifying role of conduct disorder (CD) in the association between attention-deficit/hyperactivity disorder (ADHD) and the age of onset of different stages of alcohol use. Results of linear regression analyses in unstandardized coefficients (B) and adjusted B (adj. B) with 95% confidence intervals (95% CI).

Univariable model	**Alcohol initiation**			**Regular alcohol use**			**Alcohol use disorder**		
	B	**(95% CI)**	**p**	**B**	**(95% CI)**	**p**	**B**	**(95% CI)**	**p**
ADHD	-1.07	(-1.99; -0.15)	0.02	-1.12	(-1.82; -0.41)	0.002	0.74	(-1.88; 3.36)	0.58
Multivariable model	**Alcohol initiation**			**Regular alcohol use**			**Alcohol use disorder**		
	Adj. B	**(95% CI)** [a]	**p**	**Adj. B**	**(95% CI)** [a]	**p**	**Adj. B**	**(95% CI)** [a]	**p**
Step 1									
ADHD	-0.71	(-1.55; 0.13)	0.10	-0.56	(-1.19; 0.06)	0.08	1.02	(-1.27; 3.30)	0.38
Step 2									
ADHD	-0.54	(-1.39; 0.31)	0.22	-0.38	(-1.14; 0.38)	0.33	1.42	(-1.00; 3.83)	0.25
CD	-0.51	(-1.17; 0.14)	0.13	-0.54	(-1.21; 0.13)	0.11	-1.60	(-2.62; -0.58)	0.002
Step 3									
ADHD & CD	0.44	(-1.51; 2.38)	0.66	1.17	(-0.43; 2.77)	0.15	-2.99	(-7.69; 1.70)	0.21

[a] Analyses were controlled for age and gender.

DISCUSSION

To our knowledge, the present study is the first to examine the association between ADHD and (onset of) different stages of alcohol use, while taking into account the mediating and modifying role of CD, in a representative sample of the general adult population. The NEMESIS-2 prevalence rates of ADHD (2.9%), CD (5.6%), and AUD (19.0%) are somewhat lower than in the US National Comorbidity Survey Replication [37], but they are within the range of rates that are observed worldwide [38;39].

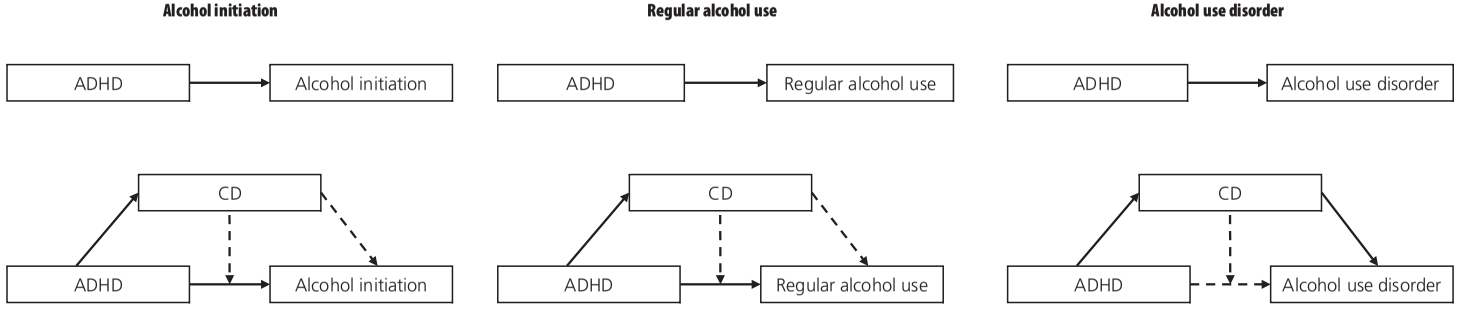
The association between ADHD, CD, and prevalence of alcohol use (disorder)

A summary of the results with regard to the prevalence of alcohol use (disorder) is given in Figure 2.1a. ADHD was associated with alcohol initiation and regular alcohol use, but not with AUD, when CD was taken into account. These results are in accordance with one [5], but not with other [12;23], prospective studies. Neither the association between ADHD and alcohol initiation nor the association between ADHD and regular alcohol use was mediated by CD. CD did mediate the association between ADHD and AUD. As in other research [20], it was observed that diagnoses of ADHD predated diagnoses of CD, and both diagnoses predated diagnoses of AUD. This strongly suggests that the role of CD as a covariate in the multivariable models represents a mediator and not just some unspecified form of confounding. This finding is in agreement with some prospective studies that examined the mediating role of CD in the association between ADHD and substance use [15;23-25].

It should be noted that initiation of (regular) alcohol use is very common and that regular alcohol use belongs to the normal range of accepted behaviors in Western societies, and therefore these behaviors cannot be interpreted as an indication of a behavioral abnormality related to the presence of ADHD (even though these behaviors occur more often in people with ADHD). The differential role of CD in the association between ADHD and the three stages of alcohol use suggests that the mediating role of CD becomes stronger over time and is associated with more pathological aspects of alcohol use. Notably, this externalizing pathway could be influenced by other factors as well, such as parenting style and peer factors [40;41]. Nevertheless, the maintained developmental pathway stresses the importance of early interventions among children with ADHD to prevent progress from ADHD into CD and subsequent AUD.

Previous studies [1;12;21;22] have reported conflicting findings with regard to the idea that children with ADHD and CD constitute a distinct group that is at extra risk of AUD. We found no evidence for this proposition in an adult sample: the combination of ADHD and CD did not result in a higher risk of alcohol use (disorder) as compared to the sum of the separate effects of ADHD and CD. The small number of individuals with both ADHD and CD (n = 21) may have complicated these findings. However, neither large confidence intervals nor trends in the hypothesized direction were observed, which supports our conclusion that CD is not very likely to play a modifying role.

a) Association between attention-deficit/hyperactivity disorder (ADHD) and the prevalence of different stages of alcohol use without and with the role of conduct disorder (CD)



b) Association between ADHD and age of onset of different stages of alcohol use without and with the role of CD

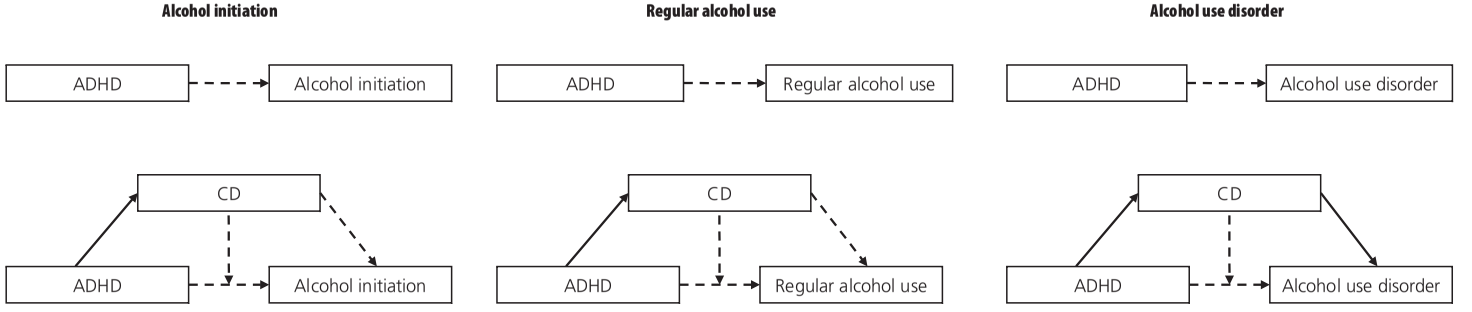


Figure 2.1. Summary of results adjusted for gender and age. Dashed lines indicate no significant association, solid lines indicate significant associations.

The association between ADHD, CD, and age of onset of alcohol use (disorder)

In accordance with previous research [6;9], we found that ADHD was associated with an earlier age of alcohol initiation and of regular alcohol use. However, in contrast to other studies [7;8], our results showed no association between ADHD and onset of AUD. Notably, the association between ADHD and onset of alcohol initiation and regular alcohol use was no longer present when age and gender were added to the model. It thus seems that previous studies, in which no correction for age and gender was made, mistakenly concluded that ADHD was associated with an earlier age of alcohol use.

Neither a mediating nor modifying role of CD was found with regard to the association between ADHD and onset of alcohol use (disorder). However, CD was associated with an earlier onset of AUD. A summary of the results with regard to the onset of alcohol use (disorder) is given in Figure 2.1b.

Limitations

A few cautionary remarks should be made with regard to the current findings. A restriction of this study concerns the relatively small number of individuals with a diagnosis of ADHD, CD or AUD, which may have caused a lack of statistical power. However, the present study used a large population based sample. This enabled us to compare relatively small numbers of diagnosed individuals with large numbers of undiagnosed individuals. The many significant associations as well as the generally narrow confidence intervals suggest that statistical power was sufficient.

Previous research among adolescents showed that the three ADHD subtypes (i.e. inattentive, hyperactive, and combined) had different associations with AUD [5;42]. However, due to the small amount of respondents with ADHD in present study we were not able to assess the possible differential contribution of the three ADHD subtypes. Also, we were unable to conduct separate analyses for alcohol abuse and dependence. Only a small group of respondents developed alcohol dependence, which is characterized by different symptoms as well as a higher symptom count than alcohol abuse (number of criteria occurring within a 12-month period ≥ 3 in dependence vs. ≥ 1 in abuse). The associations with ADHD and CD could thus be different for both AUDs. Previous research suggested, however, that this is not the case [23].

Diagnoses of ADHD, CD, and AUD were based on retrospective reports, as is often the case in population studies. Retrospective assessment could have resulted in recall bias. However, it is unclear how this would affect the presented associations. In accordance with earlier research [29], we choose to restrict our sample to respondents aged 18-44 to minimize problems with recall bias.

Approaches using multi-informant information could have resulted in other prevalence rates of ADHD as compared to the self-reports that were used in present research. However, an earlier comparison between adult self-reports and informant

reports of childhood and adult ADHD showed fairly strong associations between the two [43]. The use of self-reports in present research seems therefore justified.

Implications

Notwithstanding the potential limitations, this study helps to understand how ADHD is associated with alcohol use (disorder), and how CD affects this association. Replication of the current findings is needed, preferably in longitudinal design, so that the progression from ADHD to CD and subsequent to AUD can be further examined.

The current paper treated ADHD, CD, and AUD as separate disorders. However, some studies have suggested that these disorders reflect a general dimension of externalizing behavior [44;45]. Future research should study this dimension and the possibility that current findings of mediation represent a phenotypic phased expression of this partially genetically determined [45-47] and partially non-genetically determined [48] externalizing factor. It should be noted that AUDs are more prevalent than CD and that CD is more prevalent than ADHD. Therefore, the development of AUDs cannot be fully explained by this specific (externalizing) pathway, so other pathways must be operating as well, either as some non-ADHD or non-CD like expression of the underlying externalizing vulnerability or along some internalizing vulnerability factor with AUDs more likely to be a consequence of self-medication for existing anxiety or mood disorders [49-52].

Also, important clinical implications can be derived from the current results. The mediating role of CD in the association between ADHD and AUD indicates that treatment of children with ADHD must comprise prevention measures of both CD and AUD. Specifically, ADHD usually precedes the other two disorders and children with ADHD are often still young when they come into treatment. This creates opportunities to deal with early disruptive behavior [53;54] and to prevent CD and AUD to develop. It thus seems essential that adequate prevention measures are devised and examined for children with ADHD so that adverse outcomes can be avoided.

REFERENCES

1. Knop J., Penick E. C., Nickel E. J., Mortensen E. L., Sullivan M. A., Murtaza S. *et al.* Childhood ADHD and conduct disorder as independent predictors of male alcohol dependence at age 40. *J Stud Alcohol Drugs* 2009; **70**: 169-77.
2. Barkley R. A., Fischer M., Edelbrock C. S., Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry* 1990; **29**: 546-57.
3. Arias A. J., Gelernter J., Chan G., Weiss R. D., Brady K. T., Farrer L. *et al.* Correlates of co-occurring ADHD in drug-dependent subjects: Prevalence and features of substance dependence and psychiatric disorders. *Addict Behav* 2008; **33**: 1199-207.
4. Glantz M. D., Anthony J. C., Berglund P. A., Degenhardt L., Dierker L., Kalaydjian A. *et al.* Mental disorders as risk factors for later substance dependence: Estimates of optimal prevention and treatment benefits. *Psychol Med* 2009; **39**: 1365-77.

5. Elkins I. J., McGue M., Iacono W. G. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Arch Gen Psychiatry* 2007; **64**: 1145-52.
6. Milberger S., Biederman J., Faraone S. V., Wilens T., Chu M. P. Associations between ADHD and psychoactive substance use disorders: Findings from a longitudinal study of high-risk siblings of ADHD children. *Am J Addict* 1997; **6**: 318-29.
7. Biederman J., Wilens T. E., Mick E., Faraone S. V., Spencer T. Does attention-deficit hyperactivity disorder impact the developmental course of drug and alcohol abuse and dependence? *Biol Psychiatry* 1998; **44**: 269-73.
8. Schubiner H., Tzelepis A., Milberger S., Lockhart N., Kruger M., Kelley B. J. *et al.* Prevalence of attention-deficit/hyperactivity disorder and conduct disorder among substance abusers. *J Clin Psychiatry* 2000; **61**: 244-51.
9. Sartor C. E., Lynskey M. T., Heath A. C., Jacob T., True W. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. *Addiction* 2007; **102**: 216-25.
10. Lee S. S., Humphreys K. L., Flory K., Liu R., Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: A meta-analytic review. *Clin Psychol Rev* 2011; **31**: 328-41.
11. King S. M., Iacono W. G., McGue M. Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction* 2004; **99**: 1548-59.
12. Disney E. R., Elkins I. J., McGue M., Iacono W. G. Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. *Am J Psychiatry* 1999; **156**: 1515-21.
13. Charach A., Yeung E., Climans T., Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: Comparative meta analyses. *J Am Acad Child Adolesc Psychiatry* 2011; **50**: 9-21.
14. Langley K., Fowler T., Ford T., Thapar A. K., van den Bree M., Harold G. *et al.* Adolescent clinical outcomes for young people with attention-deficit hyperactivity disorder. *Br J Psychiatry* 2010; **196**: 235-40.
15. Brook J. S., Duan T., Zhang C., Cohen P. R., Brook D. W. The association between attention deficit hyperactivity disorder in adolescence and smoking in adulthood. *Am J Addict* 2008; **17**: 54-9.
16. Hurtig T., Ebeling H., Taanila A., Miettunen J., Smalley S., McGough J. *et al.* ADHD and comorbid disorders in relation to family environment and symptom severity. *Eur Child Adolesc Psychiatry* 2007; **16**: 362-9.
17. Nock M. K., Kazdin A. E., Hiripi E., Kessler R. C. Prevalence, subtypes, and correlates of DSM-IV conduct disorder in the National Comorbidity Survey Replication. *Psychol Med* 2006; **36**: 699-710.
18. Molina B. S. G., Pelham W. E., Gnagy E. M., Thompson A. L., Marshal M. P. Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. *Alcohol Clin Exp Res* 2007; **31**: 643-54.
19. Biederman J., Mick E., Faraone S. V., Burback M. Patterns of remission and symptom decline in conduct disorder: A four-year prospective study of an ADHD sample. *J Am Acad Child Adolesc Psychiatry* 2001; **40**: 290-8.
20. Kuperman S., Schlosser S. S., Kramer J. R., Bucholz K., Hesselbrock V., Reich T. *et al.* Developmental sequence from disruptive behavior diagnosis to adolescent alcohol dependence. *Am J Psychiatry* 2001; **158**: 2022-6.
21. Molina B. S. G., Bukstein O. G., Lynch K. G. Attention-deficit/hyperactivity disorder and conduct disorder symptomatology in adolescents with alcohol use disorder. *Psychol Addict Behav* 2002; **16**: 161-4.
22. Flory K., Milich R., Lynam D. R., Leukefeld C., Clayton R. Relation between childhood disruptive behavior disorders and substance use and dependence symptoms in young

adulthood: individuals with symptoms of attention-deficit/hyperactivity disorder and conduct disorder are uniquely at risk. *Psychol Addict Behav* 2003; **17**: 151-8.

23. Fergusson D. M., Horwood L. J., Ridder E. M. Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: Results of a 25-year longitudinal study. *Drug Alcohol Depend* 2007; **88**: S14-S26.
24. Brook D. W., Brook J. S., Zhang C., Koppel J. Association between attention-deficit/hyperactivity disorder in adolescence and substance use disorders in adulthood. *Arch Pediatr Adolesc Med* 2010; **164**: 930-4.
25. Milberger S., Biederman J., Faraone S. V., Chen L. ADHD is associated with early initiation of cigarette smoking children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1997; **36**: 37-44.
26. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. Washington, DC: American Psychiatric Association (APA); 1994.
27. de Graaf R., ten Have M., van Dorsselaer S. The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. *Int J Methods Psychiatr Res* 2010; **19**: 125-41.
28. Haro J. M., Arbabzadeh-Bouchez S., Brugha T. S., De Girolamo G., Guyer M. E., Jin R. *et al.* Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. *Int J Methods Psychiatr Res* 2006; **15**: 167-80.
29. Kessler R. C., Angermeyer M., Anthony J. C., de Graaf R., Demyttenaere K., Gasquet I. *et al.* Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* 2007; **6**: 168-76.
30. Fayyad J., de Graaf R., Kessler R., Alonso J., Angermeyer M., Demyttenaere K. *et al.* Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *Br J Psychiatry* 2007; **190**: 402-9.
31. Hasin D. S., Stinson F. S., Ogburn E., Grant B. F. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2007; **64**: 830-42.
32. Kleinbaum D. G., Klein M. *Survival Analyses. A self-learning text.* New York: Springer; 1996.
33. Sobel M. E. Some new results on indirect effects and their standard errors in covariance structure models. In: Tuma N., editor. *Sociological Methodology*. Washington, DC: American Sociological Association; 1986. p. 159-86.
34. MacKinnon D. P., Dwyer J. H. Estimating mediated effects in prevention studies. *Eval Rev* 1993; **17**: 144-58.
35. Ahlbom A., Alfredsson L. Interaction: A word with two meanings creates confusion. *Eur J Epidemiol* 2005; **20**: 563-4.
36. Rothman K. J. *Epidemiology. An Introduction.* New York: Oxford University Press; 2002.
37. Kessler R. C., Berglund P., Demler O., Jin R., Merikangas K. R., Walters E. E. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 593-602.
38. Kessler R. C., Üstün T. B. *The WHO World Mental Health Surveys. Global Perspectives on the Epidemiology of Mental Disorders*. New York: Cambridge University Press; 2008.
39. Teesson M., Hall W., Slade T., Mills K., Grove R., Mewton L. *et al.* Prevalence and correlates of DSM-IV alcohol abuse and dependence in Australia: Findings of the 2007 National Survey of Mental Health and Wellbeing. *Addiction* 2010; **105**: 2085-94.
40. Marshal M. P., Molina B. S. G. Antisocial Behaviors Moderate the Deviant Peer Pathway to Substance Use in Children With

ADHD. *J Clin Child Psychol* 2006; **35**: 216-26.

41. Johnston C., Jassy J. S. Attention-deficit/hyperactivity disorder and oppositional/conduct problems: Links to parent-child interactions. *J Can Acad Child Adolesc Psychiatry* 2007; **16**: 74-9.
42. Molina B. S. G., Pelham W. E., Jr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *J Abnorm Psychol* 2003; **112**: 497-507.
43. Murphy P., Schachar R. Use of self-ratings in the assessment of symptoms of attention deficit hyperactivity disorder in adults. *Am J Psychiatry* 2000; **157**: 1156-9.
44. White H. R., Xie M., Thompson W., Loeber R., Stouthamer-Loeber M. Psychopathology as a predictor of adolescent drug use trajectories. *Psychol Addict Behav* 2001; **15**: 210-8.
45. Kendler K. S., Prescott C. A., Myers J., Neale M. C. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry* 2003; **60**: 929-37.
46. Kendler K. S., Kuo P. H., Webb B. T., Kalsi G., Neale M. C., Sullivan P. F. *et al.* A joint genomewide linkage analysis of symptoms of alcohol dependence and conduct disorder. *Alcohol Clin Exp Res* 2006; **30**: 1972-7.
47. Hicks B. M., Bernat E., Malone S. M., Iacono W. G., Patrick C. J., Krueger R. F. *et al.* Genes mediate the association between P3 amplitude and externalizing disorders. *Psychophysiol* 2007; **44**: 98-105.
48. Knopik V. S., Heath A. C., Bucholz K. K., Madden P. A. F., Waldron M. Genetic and environmental influences on externalizing behavior and alcohol problems in adolescence: A female twin study. *Pharmacol Biochem Behav* 2009; **93**: 313-21.
49. Bolton J., Cox B., Clara I., Sareen J. Use of Alcohol and Drugs to Self-Medicate Anxiety Disorders in a Nationally Representative Sample. *J Nerv Ment Dis* 2006; **194**: 818-25.
50. Boschloo L., Vogelzangs N., Smit J. H., van den Brink W., Veltman D. J., Beekman A. T. F. et al. The performance of the Alcohol Use Disorder Identification Test (AUDIT) in detecting alcohol abuse and dependence in a population of depressed or anxious persons. *J Affect Disord* 2010; **126**: 441-6.
51. Dawson D. A., Goldstein R. B., Moss H. B., Li T. K., Grant B. F. Gender differences in the relationship of internalizing and externalizing psychopathology to alcohol dependence: Likelihood, expression and course. *Drug Alcohol Depend* 2010; **112**: 9-17.
52. Robinson J. A., Sareen J., Cox B. J., Bolton J. M. Correlates of self medication for anxiety disorders: Results From the National Epidemiolgic Survey on Alcohol and Related Conditions. *J Nerv Ment Dis* 2009; **197**: 873-8.
53. Zonnevylle-Bender M. J. S., Matthys W., Van De Wiel N. M. H., Lochman J. E. Preventive Effects of Treatment of Disruptive Behavior Disorder in Middle Childhood on Substance Use and Delinquent Behavior. *J Am Acad Child Adolesc Psychiatry* 2007; **46**: 33-9.
54. Mannuzza S., Klein R. G., Truong N. L., Moulton J. L., III, Roizen E. R., Howell K. H. *et al.* Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: Prospective follow-up into adulthood. *Am J Psychiatry* 2008; **165**: 604-9.

Chapter 3

The relationship between excessive alcohol consumption and alcohol use disorders according to DSM-IV and DSM-5

ABSTRACT

Background

Although it seems intuitive that alcohol use disorders (AUDs) include excessive alcohol consumption (EAC), this notion is not well-established. This study investigates to which degree EAC (defined as > 14/21 drinks weekly for women/men *and* at least three 5+ drinking days per week) and AUD overlap and whether problematic alcohol use groups (EAC-only, AUD-only, and EAC + AUD) differ from each other and from nonproblematic alcohol users regarding sociodemographics, mental health problems, functioning, and service utilization.

Methods

Data were derived from the Netherlands Mental Health Survey and Incidence Study-2, a population-based study including 5,443 current drinkers (aged 18-64) interviewed with the Composite International Diagnostic Interview 3.0. Both DSM-IV AUDs and a proxy of DSM-5 AUD are considered.

Results

Of the current drinkers, 3.8% reported 12-month EAC. Twelve-month prevalence of DSM-IV and DSM-5 AUD were 5.4 and 4.4%, respectively. Regarding DSM-IV, only 17.7% of subjects with AUD reported EAC and 25.3% of those with EAC had an AUD. Compared with nonproblematic alcohol users, the three groups of problematic alcohol use (EAC-only, AUD-only, and EAC + AUD) were more often associated with mental health problems, poorer functioning, and service utilization. There were few differences between EAC-only and AUD-only regarding these correlates. However, EAC + AUD had strongest associations with above-mentioned correlates compared with the other three groups. Compared with DSM-IV findings, DSM-5 AUDs had slightly larger overlap with EAC, but correlates were similarly associated with problematic alcohol use groups.

Conclusions

Findings indicate limited overlap between EAC and AUD. Yet, both dimensions were similarly associated with other problems suggesting that both should be included in future epidemiological research to detect the total group of problematic alcohol users.

Marlous Tuithof, Margreet ten Have, Wim van den Brink, Wilma Vollebergh, Ron de Graaf

Published in Alcoholism: Clinical and Experimental Research (2014) 38: 249-256.

INTRODUCTION

Psychiatric classification systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) [1], describe alcohol use disorders (AUDs) as maladaptive patterns of alcohol use leading to significant impairment and distress. Excessive drinking, which can be distinguished into high average alcohol consumption and frequent heavy drinking days, is another dimension of problematic alcohol use. The two types of excessive drinking are each associated with serious health risks [2] and with alcohol-related problems [3;4]. Co-occurrence of both types of excessive drinking may point to a small but serious group of alcohol users with a severe problematic drinking pattern in itself [5]. In the remainder of this article, excessive alcohol consumption (EAC) will refer to this combination of excessive drinking types.

Although excessive drinking is not part of the AUD diagnosis, it could be argued that it is necessary for development of alcohol-related problems and therefore is an implicit characteristic of people with AUDs. However, this notion was not supported by findings from the first Netherlands Mental Health Survey and Incidence Study (NEMESIS-1) [6]. Only one-third of the individuals with DSM-III-R alcohol abuse and half of those with alcohol dependence exceeded safe weekly drinking limits (> 14/21 drinks weekly for women/men). Also the other way around, only one-third of the drinkers exceeding these safe weekly limits met DSM-III-R criteria for an AUD. Other studies also observed a limited overlap between excessive drinking types and alcohol-related problems [3;4]. Moreover, the overlap between AUD and excessive drinking could become even smaller than the overlap reported in previous studies if excessive drinking is defined as a combination of high average alcohol consumption *and* frequent heavy drinking days (i.e., EAC).

Examining the two dimensions of problematic alcohol use (EAC and AUD) in relation to each other is not only useful to gain insight in the degree of their overlap, but also to increase understanding regarding correlates of groups of problematic users; that is, excessive drinkers without alcohol-related problems (EAC-only), people with alcohol-related problems without excessive drinking (AUD-only), and people with both aspects of problematic alcohol use (EAC + AUD). Many studies only use one dimension, but this has two important limitations. First, not all problematic alcohol users will then be included. For example, if only AUD is measured, excessive drinkers who do not meet DSM AUD criteria are overlooked, even though they might have similar problems in other areas of their life, for example, regarding mental health or functioning. Second, differences between AUD with or without excessive drinking cannot be detected, while mental health, functioning, and service utilization may be more severely affected in those with the combination of AUD and excessive drinking. Moreover, knowledge regarding associated sociodemographic characteristics may help targeting prevention at those at risk of more severe pathology.

Previous research provides some information regarding characteristics of the subgroups of problematic alcohol use. Sacco et al. [7] observed that elderly people (60+) with the combination of at-risk drinking and alcohol abuse-dependence symptoms more often had 12-month depression and poorer functioning than people with only at-risk drinking. However, both excessive drinking and AUDs are associated with younger age [8;9], and therefore, the findings of Sacco et al. [7] cannot be generalized to the general population. Another study observed that rates of psychiatric disorders were higher among at-risk drinkers than among moderate drinkers or abstainers, but lower than among people with alcohol dependence [10]. This study did not distinguish between dependence with and without at-risk drinking, but previous research suggested that comorbid psychiatric disorders may be stronger related to EAC than to symptoms caused by excessive consumption [11]. Conceivably, a gradient can be expected with people with AUD-only being least affected in other areas of their life, people with EAC + AUD being most affected and people with EAC-only being in between.

Using data from the second NEMESIS study (NEMESIS-2), we aim to examine (i) to which degree EAC and AUD overlap; and if this overlap is limited, (ii) whether problematic alcohol use groups (EAC-only, AUD-only, EAC + AUD) differ from each other and from nonproblematic alcohol users regarding various correlates, such as demographics, mental health, functioning, and service utilization. We expect that the three groups of problematic alcohol users are stronger associated with unfavorable outcomes than nonproblematic alcohol users [7;10], that EAC-only is stronger associated with unfavorable outcomes than AUD-only [11], and that EAC + AUD has the strongest associations with negative outcomes [7]. To increase the power of our analyses, we combined DSM-IV abuse and dependence. In this paper, EAC is present if two types of excessive drinking co-occur, high average alcohol consumption (> 14/21 drinks weekly for women/men) *and* frequent heavy drinking days (at least three 5+ drinking days per week). However, to increase our understanding of the overlap between EAC and AUD, we also looked at the overlap between separate excessive drinking types (high average alcohol consumption vs. frequent heavy drinking days) and separate AUDs (alcohol abuse vs. alcohol dependence). Because we are additionally interested in whether the relationship between EAC and AUD varies according to different DSM editions, we investigate our research questions separately for DSM-IV and for a proxy of proposed DSM-5 AUD.

MATERIALS AND METHODS

Sample and assessment procedures

NEMESIS-2 is a psychiatric epidemiologic survey in the Dutch general population. It is based on a multistage, stratified, random sampling of households, with one respondent randomly selected in each household. Data were collected between November 2007 and

July 2009 [12]. This resulted in a total sample of 6,646 adults aged 18 to 64 (response: 65.1%). For the present analyses, those respondents who consumed at least one drink in the year preceding the interview were included (n = 5,443). The Composite International Diagnostic Interview (CIDI) 3.0 was used to determine the presence of EAC and of mental disorders. The CIDI is a fully structured, lay administered interview developed by the World Health Organization, which is used worldwide. Clinical reappraisal interviews showed that it has generally good validity [13].

Alcohol use disorder. All respondents entered the alcohol section of the CIDI that assessed lifetime presence of symptoms of alcohol abuse, alcohol dependence, and craving. Moreover, respondents were asked whether symptoms of abuse or symptoms of dependence were still present in the past year and to rate impairment due to these symptoms. Computerized CIDI algorithms were used to generate 12-month DSM-IV abuse and dependence diagnoses. DSM-5 AUD symptoms include 3 of the 4 DSM-IV alcohol abuse (without legal problems) and all 7 DSM-IV alcohol dependence criteria complemented with a new criterion covering craving. With 2 or more of 11 symptoms subjects meet criteria for AUD [14]. All DSM-5 AUD symptoms were assessed using the CIDI 3.0 even though CIDI 3.0 was designed to yield DSM-IV diagnoses. Like DSM-IV, DSM-5 requires time clustering of symptoms, that is, the minimally required number of DSM-5 AUD symptoms must have occurred within the same 12-month period. In most cases, information regarding clustering of DSM-5 symptoms was not available as only clustering of 3 out of 7 DSM-IV dependence symptoms was assessed in the CIDI 3.0. This means that clustering of ≥ 2 alcohol abuse symptoms was not measured. Therefore, we could only construct a proxy of proposed DSM-5 AUD, using a symptom count without including a clustering criterion.

Excessive alcohol consumption. Twelve-month EAC was present when respondents reported both high average alcohol consumption *and* frequent heavy drinking days. *High average alcohol consumption* was defined as drinking more than the international acknowledged safe drinking guidelines. Specifically, > 14 drinks (standard drinks consisting of about 10 g of pure alcohol) weekly for women and > 21 drinks weekly for men [15;16; 6;]. This was based on two questions: "In the past 12 months, how often did you usually have at least one drink – every day, nearly every day, 3 to 4 days a week, 1 to 2 days a week, 1 to 3 days a month, or less than once a month?" and "On the days you drank in the past 12 months, about how many drinks did you usually have per day?". *Frequent heavy drinking days*, defined as heavy volume drinking several times a week [17;18], was present if people consumed 5+ drinks on at least three days a week. This was based on the question "How often in the past 12 months, did you have 5 or more drinks on a single day?". By this question, it was not possible to define different thresholds of a heavy drinking day for women and men.

Demographics. These included gender, age, educational level (4 categories: primary, basic vocational/lower secondary/higher secondary/higher professional, university), cohabitation status (living with a partner or not), employment status (in paid employment or not), and individual income (3 categories: low/middle/high).

Mental health. The construction of DSM-IV mental disorder diagnoses with the CIDI 3.0 has been described in detail elsewhere [12]. The following mental disorders were included in this study: mood (major depression, dysthymia, bipolar disorder), anxiety (panic disorder, agoraphobia, social phobia, specific phobia, generalized anxiety disorder), drug use (drug abuse and dependence), childhood disorder (attention-deficit/hyperactivity disorder, conduct disorder, oppositional-defiant disorder) and antisocial personality disorder. To increase accuracy of retrospective recall, childhood disorders were only assessed among respondents aged 18-44 [19]. Also, suicidal thoughts were included.

Functioning and service use. Functioning in the past month was based on the SF-36 [20;21]. The eight SF-36 scales were combined in two scales: physical functioning (general health, physical health, physical functioning, and bodily pain; $\alpha = 0.78$) and mental functioning (psychological health, psychological functioning, social functioning, and vitality; $\alpha = 0.78$), which ranged from 0 (poor) to 100 (good). Service use refers to 12-month utilization of primary care, specialized mental health care, and addiction care for emotional or addiction problems.

Data Analysis

Analyses were performed using Stata, version 11.1 [22], which enabled us to control for the complex sampling and recruitment procedure of the study. The data were weighted to ensure they were representative of the national population. First, the overlap between EAC and AUD and the prevalence of problematic alcohol use groups were established (Tables 3.1 - 3.3). Multinomial logistic regression models were conducted to test group differences regarding demographics, mental health, functioning, and service use, adjusted for gender and age (Table 3.4). Stata produces relative risk ratios in multinomial regression analyses. According to Stata, these relative risk ratios should be interpreted as the risk of the particular group relative to the base group [23], and they are thus very similar to odds ratios (ORs). To examine whether our definition of EAC influenced the results, sensitivity analyses were carried out with less stringent definitions of EAC; that is frequent heavy drinking days *or* high average alcohol consumption; or *one* heavy drinking day per week and high average alcohol consumption. Level of significance was set at 0.05.

RESULTS

Prevalence of EAC and AUD and their overlap

Table 3.1 shows prevalence of excessive drinking patterns and AUDs. Of the total population, 7.7% reported high average alcohol consumption, 6.4% frequent heavy drinking days, and 3.8% both types of excessive drinking, that is, EAC in the past year. Twelve-month DSM-IV alcohol abuse was present in 4.5% of the respondents and alcohol dependence in 0.9% (in total 5.4% reported a DSM-IV AUD). Twelve-month DSM-5 AUD was about 20% less prevalent than DSM-IV AUD: 4.4% reported a DSM-5 AUD.

Table 3.1. Twelve-month prevalence of excessive drinking patterns and alcohol use disorders among 5,443 current drinkers in unweighted counts and weighted percentages.

	n	%
Excessive drinking patterns		
High average alcohol consumption	426	7.7
Frequent heavy drinking days	328	6.4
Excessive alcohol consumption [a]	210	3.8
Alcohol use disorders		
DSM-IV		
Alcohol abuse	190	4.5
Alcohol dependence	35	0.9
Any alcohol use disorder	225	5.4
DSM-5 alcohol use disorder	197	4.4

[a] Excessive alcohol consumption consists of high average alcohol consumption (> 14/21 drinks weekly for women/men) *and* frequent heavy drinking days (at least three 5+ drinking days per week).

As shown in Table 3.2, only 17.7% of those with DSM-IV AUD reported EAC and 25.1% of subjects with EAC met criteria of DSM-IV AUD (Cohen's Kappa = 0.17). Notably, the proportion of EAC was considerably smaller for those with alcohol abuse (10.4%) than for those with alcohol dependence (54.7%). Compared with DSM-IV AUD, the overlap between EAC and DSM-5 AUD was slightly higher: 25.3% of those with DSM-5 AUD reported EAC and 29.2% of subjects with EAC had a DSM-5 AUD (Cohen's Kappa = 0.24).

Table 3.2. The overlap between excessive drinking patterns and AUD among 5,443 current drinkers in unweighted counts and weighted percentages.

	DSM-IV AUD			DSM-5 AUD
	AA	AD	AUD	
HAAC				
% of HAAC with reported disorder	12.1	7.0	19.1	23.7
Unweighted n	40	23	63	83
% of reported disorder with HAAC	20.6	60.9	27.3	41.8
FHDD				
% of FHDD with reported disorder	13.2	7.7	20.9	20.5
Unweighted n	33	20	53	61
% of reported disorder with FHDD	18.7	55.0	24.7	29.9
EAC [a]				
% of EAC with reported disorder	12.3	12.8	25.1	29.2
Unweighted n	22	19	41	54
% of reported disorder with EAC	10.4	54.7	17.7	25.3

Note. AUD: alcohol use disorder; AA: alcohol abuse; AD: alcohol dependence; HAAC: high average alcohol consumption; FHDD: frequent heavy drinking days; EAC: excessive alcohol consumption.
[a] EAC consists of HAAC (> 14/21 drinks weekly for women/men) *and* FHDD (at least three 5+ drinking days per week).

Four groups were created by combining EAC and AUD, separately for DSM-IV and DSM-5 (Table 3.3). The majority of the population belonged to the first group, including nonproblematic alcohol users with no EAC and no AUD (DSM-IV: 91.7%; DSM-5: 92.9%). Less than 3% belonged to the second group (EAC-only). The third group (AUD-only) was larger for DSM-IV (4.5%) than for DSM-5 (3.3%). The fourth group, consisting of people with both dimensions of problematic alcohol use (EAC + AUD) was remarkably small (DSM-IV: 1.0%; DSM-5: 1.1%).

Table 3.3. Groups of problematic alcohol use among 5,443 current drinkers in unweighted counts and weighted percentages, separately for DSM-IV and DSM-5 alcohol use disorders (AUDs).

Group	EAC	AUD	DSM-IV		DSM-5	
			n	%	n	%
Group 1	No	No	5,049	91.7	5,090	92.9
Group 2	Yes	No	169	2.9	156	2.7
Group 3	No	Yes	184	4.5	143	3.3
Group 4	Yes	Yes	41	1.0	54	1.1

Note. Presence of excessive alcohol consumption (EAC) refers to high average alcohol consumption (> 14/21 drinks weekly for women/men) *and* frequent heavy drinking days (at least three 5+ drinking days per week). Presence of DSM-IV AUD refers to alcohol abuse or dependence.

Comparing DSM-IV problematic alcohol use groups

Table 3.4 portrays frequencies, means, and results of multinomial regression analyses, adjusted for age and gender. First, the three problematic alcohol use groups were each compared with nonproblematic alcohol users; thus, no EAC and no DSM-IV AUD (group 1) was the reference group. The three problematic alcohol use groups were more often male and living without a partner. On average, people with EAC-only were older than nonproblematic alcohol users, whereas people with AUD-only and EAC + AUD were younger. Additionally, in comparison with nonproblematic alcohol users, EAC-only was more strongly associated with lower and higher secondary educational level than with the highest educational level (acting as the reference group), with being unemployed and with a lower income, whereas EAC + AUD was associated with low educational level and low income.

Compared with nonproblematic alcohol users, the three problematic alcohol use groups were each more often associated with clinical correlates. Specifically, EAC-only was associated with mood (lifetime and 12-month), drug use (12-month) and childhood disorder, suicidal thoughts (lifetime), poorer physical and mental functioning, utilization of specialized mental health care and of addiction care. AUD-only was associated with 12-month anxiety, drug use (lifetime and 12 month), childhood disorder, poorer mental functioning, utilization of any health care, primary care and specialized mental health care. EAC + AUD was associated with all 12-month mental disorders, childhood and antisocial personality disorder, poorer physical and mental functioning, and all types of service utilization.

Next, comparison of AUD-only and EAC-only (sixth column of Table 3.4) showed very few differences between these 2 groups. Particularly, people with EAC-only were older and had a lower income than people with AUD-only, whereas primary care utilization was higher in people with AUD-only. No further significant differences were observed.

Lastly, comparison of the groups with (EAC + AUD) and without (EAC-only, AUD-only) overlap (the last 2 columns of Table 3.4) showed that the associations with correlates were often strongest for the EAC + AUD group. Specifically, compared with EAC-only or AUD-only, EAC + AUD was more often associated with lower education, living without a partner, 12-month anxiety disorder, 12-month suicidal thoughts, antisocial personality disorder, poorer physical functioning, and utilization of any health care. Also, EAC + AUD more often had a low income, childhood disorder, and poorer mental functioning than AUD-only. Compared with EAC-only, EAC + AUD was more often associated with younger age and 12-month utilization of primary care.

Comparing DSM-5 problematic alcohol use groups

Results regarding DSM-5 groups differed slightly from DSM-IV findings, but the same picture emerged and the same conclusions can be drawn (Table available on request). Specifically, problematic alcohol users were more often male, without a partner, more often had mental health problems, poorer physical and mental functioning, and service

Table 3.4. Correlates of 12-month DSM-IV problematic alcohol use groups in weighted percentages or weighted means among 5,443 current drinkers.

	Group 1 [a] (ref) n = 5,049	Group 2 [a] EAC-only n = 169		
	% / mean	% / mean	adj. OR	(95% CI)
Demographics				
Male gender (%)	53.1	77.8	**3.07****	(2.01; 4.69)
Mean age (18-64)	42.0	46.7	**1.03****	(1.01; 1.05)
Educational level (%)				
Primary, basic vocational	5.6	6.9	1.62	(0.81; 3.25)
Lower secondary	20.9	21.9	**1.59**	(1.04; 2.46)
Higher secondary	42.3	49.4	**1.76**	(1.10; 2.80)
Higher professional, university (ref)	31.3	21.8	1.00	-
Living without partner (%)	30.5	35.8	**1.74***	(1.16; 2.59)
Unemployed (%)	20.1	31.9	**1.88***	(1.24; 2.86)
Individual income (%)				
Low	54.0	51.8	**4.92***	(1.85; 13.08)
Middle	39.0	45.1	**3.28**	(1.22; 8.80)
High (ref)	7.0	3.2	1.00	-
Mental health				
Mood disorder (%)				
Never (ref)	80.3	73.2	1.00	-
Lifetime, not 12-month	14.1	18.7	**1.77**	(1.12; 2.80)
12-Month	5.6	8.1	**2.00**	(1.08; 3.68)
Anxiety disorder (%)				
Never (ref)	80.9	76.9	1.00	-
Lifetime, not 12-month	10.1	10.8	1.26	(0.78; 2.05)
12-Month	9.0	12.3	1.73	(0.84; 3.54)
Drug use disorder (%)				
Never (ref)	94.8	90.4	1.00	-
Lifetime, not 12-month	4.0	6.2	1.84	(0.55; 6.14)
12-Month	1.2	3.5	**4.20**	(1.07; 16.54)
Suicidal thoughts (%)				
Never (ref)	92.5	82.5	1.00	-
Lifetime, not 12-month	6.7	15.9	**2.85****	(1.59; 5.08)
12-Month	0.7	1.6	2.70	(0.86; 8.47)
Childhood disorder [b] (%)	8.3	23.0	**3.29**	(1.22; 8.84)
Antisocial personality disorder (%)	2.5	2.5	1.03	(0.32; 3.37)

Table 3.4 continues on the next page

Group 3 [a] AUD-only n = 184			Group 4 [a] EAC+AUD n = 41			Group 3 vs. Group 2	Group 4 vs. Group 2	Group 4 vs. Group 3
% / mean	adj. OR	(95% CI)	% / mean	adj. OR	(95% CI)	p	p	p
74.7	**2.66****	(1.59; 4.45)	71.5	**2.25**	(1.03; 4.89)	0.66	0.44	0.70
32.0	**0.94****	(0.92; 0.96)	32.8	**0.94***	(0.90; 0.99)	**< 0.001**	**< 0.001**	0.79
6.3	1.56	(0.70; 3.49)	15.4	**5.77***	(1.97; 16.89)	0.95	**0.04**	**0.04**
20.5	0.92	(0.52; 1.63)	38.7	**2.84**	(1.11; 7.28)	0.14	0.27	0.07
48.2	1.23	(0.79; 1.90)	29.3	1.17	(0.48; 2.83)	0.26	0.44	0.93
25.0	1.00	-	16.6	1.00	-	-	-	-
63.5	**2.26****	(1.69; 3.02)	80.5	**7.04****	(3.39; 14.60)	0.31	**< 0.001**	**0.004**
21.2	1.24	(0.72; 2.13)	23.9	1.46	(0.53; 3.97)	0.23	0.63	0.80
58.1	0.64	(0.28; 1.48)	82.4	**10.02**	(1.22; 82.11)	**0.01**	0.53	**0.02**
33.9	0.57	(0.27; 1.20)	16.5	2.41	(0.30; 19.52)	**0.01**	0.79	0.21
8.0	1.00	-	1.1	1.00	-	-	-	-
77.7	1.00	-	68.9	1.00	-	-	-	-
12.5	1.46	(0.89; 2.41)	14.6	1.83	(0.72; 4.61)	0.56	0.95	0.68
9.8	1.87	(0.93; 3.76)	16.5	**3.52**	(1.06; 11.72)	0.87	0.43	0.30
72.0	1.00	-	52.5	1.00	-	-	-	-
10.0	1.35	(0.69; 2.63)	10.5	1.92	(0.56; 6.58)	0.87	0.55	0.64
18.0	**2.64****	(1.65; 4.22)	37.0	**7.40****	(3.62; 15.13)	0.34	**0.01**	**0.01**
75.3	1.00	-	72.6	1.00	-	-	-	-
13.1	**2.51***	(1.33; 4.72)	17.1	3.60	(0.94; 13.75)	0.64	0.46	0.59
11.5	**6.97****	(2.89; 16.78)	10.3	**6.84***	(1.75; 26.72)	0.49	0.62	0.98
90.3	1.00	-	75.0	1.00	-	-	-	-
8.5	1.42	(0.74; 2.72)	9.2	1.83	(0.59; 5.65)	0.10	0.47	0.63
1.1	2.06	(0.53; 7.96)	15.8	**34.24****	(10.28; 114.00)	0.73	**0.002**	**0.002**
21.7	**2.31**	(1.17; 4.58)	48.6	**7.35****	(3.46; 15.62)	0.57	0.18	**0.02**
10.2	2.58	(0.98; 6.82)	32.1	**12.63****	(5.35; 29.85)	0.22	**0.001**	**0.01**

Table 3.4. *Continued.*

	Group 1 [a] (ref) n = 5,049	Group 2 [a] EAC-only n = 169		
	% / mean	% / mean	adj. OR	(95% CI)
Functioning (past-month)				
Mean physical functioning (0-100)	85.6	83.4	**0.99**	(0.98; 1.00)
Mean mental functioning (0-100)	85.8	83.1	**0.98***	(0.97; 0.99)
Service use (12-month)				
Any health care (%)	9.8	11.5	1.36	(0.82; 2.26)
Primary care (%)	8.4	6.6	0.87	(0.43; 1.75)
Specialized mental health care (%)	5.5	9.9	**2.13***	(1.24; 3.67)
Addiction care (%)	0.3	3.0	**9.07***	(2.01; (40.90)

Note. - Not calculated. In bold means significant at $p < 0.05$; * $p < 0.01$; ** $p < 0.001$. Excessive alcohol consumption (EAC) defined as high average alcohol consumption (> 14/21 drinks weekly for women/men) *and* frequent heavy drinking days (at least three 5+ drinking days per week); AUD: DSM-IV alcohol use disorder. Results of multinomial logistic regression analyses with odds ratios, adjusted for gender and age (adj. OR), with 95% confidence intervals (CI) and with group comparisons using p-values.

[a] Group 1 (no EAC and no AUD) is the reference group.

[b] Childhood disorders were only assessed in respondents aged 18 to 44 (n = 2,694).

utilization than nonproblematic alcohol users. Like DSM-IV, comparison of DSM-5 AUD-only and EAC-only showed that the groups were quite similar regarding associations with correlates. However, contrasting DSM-IV findings, EAC + AUD no longer differed from EAC-only and AUD-only with regard to partner status and educational level. More importantly, the contrast between groups with overlap (EAC + AUD) and without overlap (EAC-only and AUD-only) was less outspoken in terms of mental health and functioning.

Sensitivity analyses

Relaxing the EAC definition into frequent heavy drinking days *or* high average alcohol consumption; or into *one* heavy drinking day per week and high average alcohol consumption resulted in increase of the EAC + AUD group, but this group was still smaller than the AUD-only group. Moreover, the contrast between EAC + AUD and EAC-only or AUD-only became smaller and the three groups of problematic alcohol use became rather homogeneous. These results were the same for DSM-IV and DSM-5 AUDs (results are available on request).

DISCUSSION

Only a minority of the people with AUD also reported EAC in this population-based study, even though it seems intuitive that excessive drinking is needed for an AUD diagnosis.

Group 3 [a] AUD-only n = 184			Group 4 [a] EAC+AUD n = 41			Group 3 vs. Group 2	Group 4 vs. Group 2	Group 4 vs. Group 3
% / mean	adj. OR	(95% CI)	% / mean	adj. OR	(95% CI)	p	p	p
86.3	0.99	(0.98; 1.00)	75.3	**0.96***	(0.94; 0.99)	0.99	**0.03**	**0.02**
84.6	**0.99**	(0.98; 1.00)	75.8	**0.96***	(0.93; 0.99)	0.34	0.13	**0.04**
16.6	**2.07**	(1.19; 3.62)	31.7	**4.71****	(2.54; 8.74)	0.25	**0.004**	**0.05**
15.3	**2.30***	(1.28; 4.14)	27.6	**4.69****	(2.49; 8.83)	**0.03**	**0.001**	0.11
11.1	**2.39**	(1.23; 4.67)	16.2	**3.59***	(1.50; 8.58)	0.78	0.32	0.40
1.4	3.08	(0.49; 19.52)	5.5	**13.11***	(2.06; 83.54)	0.25	0.69	0.09

The problematic alcohol use groups (EAC-only, AUD-only, EAC + AUD) were each associated with adverse outcomes in mental health, functioning, and service utilization. This suggests that a large problematic group of alcohol users with serious negative outcomes is overlooked if only one dimension is taken into account. Furthermore, co-occurrence of EAC and AUD was uncommon but was associated with most vulnerability. Targeted interventions should thus focus on this group. Characteristics that may help to identify people with EAC + AUD are lower educational level, living without a partner and low income.

Limitations

EAC was based on self-report, recall bias might be an issue then. Specifically, difficulties remembering the amounts and frequencies in an average week may have resulted in an underestimation of EAC. Thus, the groups with EAC-only and EAC + AUD could be somewhat larger in reality. Recall of lifetime mental disorders can also be a source of bias [24], resulting in underestimation of their prevalence rates, but possibly also in stronger associations with the problematic alcohol use groups.

It should be noted that prevalence rates of DSM-IV alcohol abuse and dependence in NEMESIS-2 were in accordance with other European observations, but were lower than prevalence rates observed in the United States and New Zealand [25;26]. Also, the low prevalence of alcohol dependence (0.9%) relative to abuse (4.5%) differs

from findings from the United States [26], where similar prevalence rates of alcohol abuse and dependence were observed. It is uncertain how these observations affect the generalizability of the present findings. If AUD diagnoses, and especially alcohol dependence, were somewhat more restricted in the present study, their overlap with alcohol consumption could even be smaller in countries or studies with higher AUD prevalence rates.

Due to the small number of cases with alcohol dependence, we had to combine DSM-IV alcohol abuse and dependence to study correlates of problematic alcohol use. When interpreting the results, it is important to keep in mind that the overlap between EAC and AUD was considerably smaller for abuse than for dependence and that abuse cases represent the majority of the AUD-only group, whereas abuse and dependence cases are more equally represented in the EAC + AUD group.

In our study, we focused on problematic alcohol use as portrayed by severe excessive drinking, not exceeding safe drinking guidelines. Therefore, our definition of EAC was stricter than those used in other studies [7] or general drinking guidelines [27]. This means that only general comparisons are possible with other studies that focus on the relationship between exceeding safe drinking guidelines and alcohol-related problems [3;4;6;7].

DSM-5 requires that the necessary number of DSM-5 AUD symptoms must have occurred within the same 12-month period. However, as the CIDI 3.0 was designed to yield DSM-IV AUD diagnoses, information regarding clustering of symptoms was only available for 3 out of the 7 DSM-IV dependence symptoms, not for 2 out of the 11 DSM-5 AUD symptoms. Consequently, it was not possible to apply this clustering criterion in the DSM-5 diagnoses, and only a proxy of DSM-5 AUD using a symptom count could be constructed. Additional analyses showed that eliminating the clustering criterion in DSM-IV AUD increased the prevalence of alcohol dependence, but decreased the prevalence of alcohol abuse, resulting in unchanged overall AUD prevalence rates. We were not able to apply the clustering criterion for DSM-5, but we assume that this would have had a similar limited effect on DSM-5 prevalence rates.

Findings

A major finding of this study is that, even though it seems conceivable that considerable drinking is needed for an AUD diagnosis, only one-fifth of the subjects with DSM-IV AUD reported EAC. A limited overlap was also observed with less stringent definitions of EAC [3;4;6] and for the proportion of EAC in both alcohol abuse and dependence cases. Yet, compared to DSM-IV AUD, a somewhat higher proportion of people with DSM-5 AUD reported EAC. This was not surprising as mild abuse cases with only one symptom are no longer diagnosed in DSM-5 [28]. Conceivably, these mild cases were an important part of the DSM-IV AUD cases without co-occurring EAC. Nevertheless, although clinical research suggests that a persistent pattern of heavy drinking is needed

to develop AUD [29], current results indicate that AUD diagnoses in population-based studies are more inclusive, that is, non-heavy drinkers also become diagnosed with AUD.

Partly, the limited overlap between EAC and AUD may be the result of an underestimation of alcohol consumption in the present study. Also, errors in the identification of AUD symptoms in population-based research could play a role. For example, Caetano et al. [30] observed that especially symptoms regarding impairment of control and tolerance are prone to misinterpretation and may lead to overestimation of AUD prevalence rates. Yet, the limited overlap between EAC and AUD may also reflect that they represent two separate dimensions of problematic alcohol use. Apparently, due to the difference in main focus, one dimension can present itself without the presence of the other.

Notably, comparison of the three problematic alcohol use groups (EAC-only, AUD-only, EAC + AUD) with nonproblematic alcohol users showed that all problematic alcohol users more often reported mental health problems, poorer functioning, and service utilization than nonproblematic alcohol users. Thus, as expected, also the groups with only one aspect of problematic alcohol use reported serious problems in other areas of their life. This is in agreement with the literature about at-risk drinking and AUDs [8;10;31], and it implies that both dimensions should be taken into account to detect the total group of problematic alcohol users. This notion is further supported by comparison of EAC-only and AUD-only as these groups were very similar in their associations with mental health aspects. Yet, these findings also indicate that the association between psychiatric comorbidity and AUDs is not only due to alcohol consumption but also to the AUD symptoms itself, thereby contradicting our hypothesis that EAC-only would be stronger associated with unfavorable outcomes than AUD-only [11].

As expected, co-occurrence of EAC and AUD seemed to be associated with most vulnerability as it was more strongly associated with clinical correlates than EAC-only [7] or AUD-only. An especially strong association was found with 12-month suicidal thoughts. Previous research observed a relation between suicide attempts and alcohol consumption [32] and AUDs [33]. Current findings additionally suggest that in people with both AUD and an excessive drinking pattern awareness for 12-month suicidal thoughts could be worthwhile. Moreover, the strong association between EAC + AUD and 12-month mental disorders indicates that people with EAC + AUD should also be monitored for symptoms of other mental disorders [34;35].

Our results help to describe the problematic alcohol use groups with regard to sociodemographic aspects. Specifically, compared to nonproblematic alcohol users, AUD with and without EAC was more often associated with younger age [8;26;31], whereas EAC-only was more often associated with older age [10]. This suggests that older people are better capable of maintaining an excessive drinking pattern without experiencing alcohol-related DSM problems, possibly because they created a living situation in which (excessive) alcohol consumption less often triggers alcohol-related problems. The finding that EAC-only and especially EAC + AUD were related to lower

educational level, and lower income is in line with a prospective study that suggested that lower educational level predicts excessive drinking [36]. This indicates that these factors may help to identify people at risk of severe problematic alcohol use.

Implications

The observed limited overlap between EAC and AUD indicates that excessive drinking and AUD diagnoses may measure two different aspects of problematic alcohol use in population-based research. Yet, as all problematic alcohol use groups had problems in other areas, combining the two dimensions can be worthwhile in public health research to detect the total group of problematic alcohol users. Moreover, people with the combination of EAC + AUD had the most severe problems in terms of psychiatric comorbidity and social functioning. It may be worthwhile to investigate whether escalation of problems can be prevented by special attention to people with one aspect of problematic alcohol use and existing correlates of EAC + AUD, for example, low socioeconomic status and living without a partner.

The current study used cross-sectional data and it was therefore not possible to examine differences in the course of problematic alcohol use between the groups. It seems desirable to include both dimensions in future studies examining this course. Specifically, longitudinal epidemiological studies generally observe high remission rates of AUDs [37], whereas clinical studies describe AUD as a chronic relapsing disorder [29]. Perhaps, the higher rate of excessive drinking among those with AUD in clinical research compared to those in epidemiological research could play a role in this discrepancy [29;38]. Specifically, AUDs with excessive drinking may be associated with more persistency than AUDs without excessive drinking. Also, a substantial part of those who recover from AUD may still have EAC. This would imply that remission of AUD does not necessarily indicate remission of problematic alcohol use and its related health consequences. This should be examined in future longitudinal research.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. Washington, DC: American Psychiatric Association (APA); 1994.
2. World Health Organization. *International guide for monitoring alcohol consumption and related harm*. Geneva: World Health Organization (WHO); 2000.
3. Caetano R., Mills B., Pinsky I., Zaleski M., Laranjeira R. The distribution of alcohol consumption and the prevention paradox in Brazil. *Addiction* 2012; **107**: 60-8.
4. Gmel G., McKeganey N., Klingemann S., Müller R., Brenner D. Revising the preventive paradox: The Swiss case. *Addiction* 2001; **96**: 273-84.
5. Smith G. W., Shevlin M., Murphy J., Houston J. E. An assessment of the demographic and clinical correlates of the dimensions of alcohol use behaviour. *Alcohol Alcohol* 2010; **45**: 563-72.
6. Verdurmen J., Monshouwer K., van Dorsselaer S., de Graaf R. *Bovenmatig drinken in Nederland (Excessive drinking*

in the Netherlands). Utrecht: Trimbos-instituut; 2003.

7. Sacco P., Bucholz K. K., Spitznagel E. L. Alcohol use among older adults in the National Epidemiologic Survey on Alcohol and Related Conditions: A latent class analysis. *J Stud Alcohol Drugs* 2009; **70**: 829-38.
8. Hasin D. S., Stinson F. S., Ogburn E., Grant B. F. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2007; **64**: 830-42.
9. Karlamangla A., Zhou K., Reuben D., Greendale G., Moore A. Longitudinal trajectories of heavy drinking in adults in the United States of America. *Addiction* 2006; **101**: 91-9.
10. Bott K., Meyer C., Rumpf H. J., Hapke U., John U. Psychiatric disorders among at-risk consumers of alcohol in the general population. *J Stud Alcohol* 2005; **66**: 246-53.
11. Farrell M., Howes S., Bebbington P., Brugha T., Jenkins R., Lewis G. *et al.* Nicotine, alcohol and drug dependence, and psychiatric comorbidity - results of a national household survey. *Int Rev Psychiatry* 2003; **15**: 50-6.
12. de Graaf R., ten Have M., van Dorsselaer S. The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. *Int J Methods Psychiatr Res* 2010; **19**: 125-41.
13. Haro J. M., Arbabzadeh-Bouchez S., Brugha T. S., De Girolamo G., Guyer M. E., Jin R. *et al.* Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. *Int J Methods Psychiatr Res* 2006; **15**: 167-80.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Washington, DC: American Psychiatric Association (APA); 2013.
15. British Medical Association. *Alcohol Guidelines on Sensible Drinking*. London: British Medical Association (BMA), 1995.
16. Haynes J. C., Farrell M., Singleton N., Meltzer H., Araya R., Lewis G. *et al.* Alcohol consumption as a risk factor for anxiety and depression: Results from the longitudinal follow-up of the National Psychiatric Morbidity Survey. *Brit J Psychiat* 2005; **187**: 544-51.
17. Gmel G., Kuntsche E., Rehm J. Risky single-occasion drinking: bingeing is not bingeing. *Addiction* 2011; **106**: 1037-45.
18. Li T. K., Hewitt B. G., Grant B. F. The Alcohol Dependence Syndrome, 30 years later: a commentary. The 2006 H. David Archibald lecture. *Addiction* 2007; **102**: 1522-30.
19. Kessler R. C., Angermeyer M., Anthony J. C., de Graaf R., Demyttenaere K., Gasquet I. *et al.* Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* 2007; **6**: 168-76.
20. Stewart A. L., Hays R. D., Ware J. E. The MOS short-form general health survey: Reliability and validity in a patient population. *Med Care* 1988; **26**: 724-35.
21. Ware J. E., Sherbourne C. D. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473-83.
22. Statacorp. Stata Statistical Software: Release 11. College Station, Texas: Statacorp LP; 2009.
23. Gutierrez RG. Use of the term 'relative risk ratio'. http://www.stata.com/statalist/archive/2005-04/msg00678.html Archived by WebCite® at http://www.webcitation.org/6BG3PLTaK Statacorp. 2005. 8-10-2012.
24. Moffitt T. E., Caspi A., Taylor A., Kokaua J., Milne B. J., Polanczyk G. *et al.* How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. *Psychol Med* 2010; **40**: 899-909.

25. Kessler R. C., Üstün T. B. *The WHO World Mental Health Surveys. Global Perspectives on the Epidemiology of Mental Disorders*. New York: Cambridge University Press; 2008.
26. Grant B. F., Dawson D. A., Stinson F. S., Chou S. P., Dufour M. C., Pickering R. P. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug Alcohol Depend* 2004; **74**: 223-34.
27. Dawson D. A., Grant B. F. The "gray area" of consumption between moderate and risk drinking. *J Stud Alcohol Drugs* 2011; **72**: 453-8.
28. Agrawal A., Heath A. C., Lynskey M. T. DSM-IV to DSM-5: The impact of proposed revisions on diagnosis of alcohol use disorders. *Addiction* 2011; **106**: 1935-43.
29. Storbjörk J., Room R. The two worlds of alcohol problems: Who is in treatment and who is not? *Addict Res Theory* 2008; **16**: 67-84.
30. Caetano R. The identification of alcohol dependence criteria in the general population. *Addiction* 1999; **94**: 255-67.
31. Teesson M., Hall W., Slade T., Mills K., Grove R., Mewton L. *et al.* Prevalence and correlates of DSM-IV alcohol abuse and dependence in Australia: Findings of the 2007 National Survey of Mental Health and Wellbeing. *Addiction* 2010; **105**: 2085-94.
32. Kerr W. C., Subbaraman M., Ye Y. Per capita alcohol consumption and suicide mortality in a panel of US states from 1950 to 2002. *Drug Alcohol Rev* 2011; **30**: 473-80.
33. Boenisch S., Bramesfeld A., Mergl R., Havers I., Althaus D., Lehfeld H. *et al.* The role of alcohol use disorder and alcohol consumption in suicide attempts - A secondary analysis of 1921 suicide attempts. *Eur Psychiatry* 2010; **25**: 414-20.
34. Kessler R. C., Price R. H. Primary prevention of secondary disorders: A proposal and agenda. *Am J Community Psychol* 1993; **21**: 607-33.
35. Merikangas K. R., Angst J., Eaton W., Canino G. Comorbidity and boundaries of affective disorders with anxiety disorders and substance misuse: Results of an international task force. *Brit J Psychiat* 1996; **168**: 58-67.
36. van Oers J. A., Bongers I. M., van de Goor L. A., Garretsen H. F. Alcohol consumption, alcohol-related problems, problem drinking, and socioeconomic status. *Alcohol Alcohol* 1999; **34**: 78-88.
37. de Bruijn C., van den Brink W., de Graaf R., Vollebergh W. The three year course of alcohol use disorders in the general population: DSM-IV, ICD-10 and the Craving Withdrawal Model. *Addiction* 2006; **101**: 385-92.
38. Dawson D. A., Stinson F. S., Chou S. P., Grant B. F. Three-year changes in adult risk drinking behavior in relation to the course of alcohol-use disorders. *J Stud Alcohol Drugs* 2008; **69**: 866-77.

Chapter 4

Predicting persistency of DSM-5 alcohol use disorder and examining drinking patterns of recently remitted individuals:

a prospective general population study

ABSTRACT

Aims

To establish the 3-year persistency rate of alcohol use disorder (AUD) and its predictors, and to examine drinking patterns of recently remitted individuals.

Design and setting

The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) surveyed a nationally representative sample of adults (aged 18-64) at baseline (response: 65.1%) and 3-year follow-up (response: 80.4%).

Participants

People with AUD at baseline, as defined by DSM-5 (n = 198).

Measurements

AUD, drinking patterns and mental disorders were assessed using the Composite International Diagnostic Interview 3.0. Other predictors were assessed with an additional questionnaire. Predictors of persistency were examined with univariable and multivariable logistic regression analyses.

Results

The AUD persistency rate was 29.5% (95% confidence intervals (CI) = 20.0; 39.0). In the multivariable model, the older (25-34 and 35-44) age groups had lower AUD persistency (odds ratio (OR) = 0.05, 95% CI = 0.00; 0.49 and OR = 0.14, 95% CI = 0.02; 0.79, respectively) than the youngest age group (18–24). A higher number of weekly drinks and a comorbid anxiety disorder predicted AUD persistency (OR = 1.03, 95% CI = 1.00; 1.07 and OR = 4.56, 95% CI = 1.04; 20.06, respectively). Furthermore, remission was associated with a reduction of six drinks per week between T_0 and T_1. It should be noted, however, that 35.8% (95% CI = 22.4; 49.2) of people in diagnostic remission still drank more than the recommended maximum (> 7/14 drinks weekly for women/men).

Conclusions

Only a minority of people in the Netherlands with alcohol use disorder as defined by DSM-5 still have the disorder three years later. Factors that help identify people at risk of alcohol use disorder persistence are: younger age, a higher number of weekly drinks and a comorbid anxiety disorder. A substantial number of people recently in diagnostic remission still drink above the maximum recommended level.

Marlous Tuithof, Margreet ten Have, Wim van den Brink, Wilma Vollebergh, Ron de Graaf

Published in Addiction (2013) 108: 2091-2099.

INTRODUCTION

Prospective studies on the course of alcohol use disorders (AUDs) in the general population have shown relatively low persistency rates (e.g. [1-4]), indicating that AUDs are persistent in some and transient in most people. However, persistent AUDs are often associated with high personal and societal costs [5-8] and may require expensive and intensive treatment [9;10]. Therefore, it is essential to identify people at risk of AUD persistency. Furthermore, diagnostic remission does not require a change in drinking patterns. Remitted individuals could thus still drink excessively and be at risk of health problems and relapse into another episode of AUD [11-14]. Unfortunately, it is largely unknown to which degree risky drinking still occurs in recently remitted people.

Epidemiological studies have observed several correlates of AUD persistency: male gender [15;16], younger age [16-18], being single [18], more AUD symptoms [19], severity of alcohol problems [3;15;20], more alcohol consumption [19], comorbid mood and anxiety disorders [3;18;21], comorbid drug dependence [3;16], personality disorders [16], smoking [18;19] and negative life events [22]. In contrast, correlates of a transient course included treatment utilization [23] and a longer AUD duration [1]. Interpretation of these findings is impeded, as most studies were cross-sectional, with a retrospective assessment of remission [1;16;18;22;23]. Other studies were longitudinal but used general population subsamples (e.g. men [20], young adults [3], anxious or depressed people [15;21]), thus preventing inferences about the general population. The only exceptions are longitudinal findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a prospective study including a nationally representative sample of US adults with a 3-year follow-up period [4;17;19]. Thus, more information derived from longitudinal population-based research seems desirable.

In previous studies, approximately one-quarter of people in remission from life-time AUD currently had risky drinking patterns (for women defined > 7 drinks weekly or 4+ drinks on any day and for men > 14 drinks weekly or 5+ drinks on any day) [12;24]. They are at increased risk of alcohol-related diseases and relapse into another episode of AUD [12;13]. However, findings regarding lifetime remitters cannot be generalized to recent remitters. Specifically, as successful long-term remission is associated with lower drinking levels [12], conceivably a smaller proportion of risk drinkers is observed in lifetime, including long-term successful, remitters than in recent remitters. Thus, despite the overall decreased drinking levels associated with AUD remission [25], an important proportion may still drink excessively, and this subgroup is important for relapse prevention.

This study investigates predictors of AUD persistency and drinking patterns of recently remitted people. Using data from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), our aims are threefold: to (i) assess the 3-year AUD persistency rate in the general population; (ii) predict 3-year AUD persistency using a wide variety of predictors including sociodemographics, clinical AUD characteristics,

drinking characteristics, psychiatric comorbidity and vulnerability factors; and (iii) assess drinking patterns of people in recent diagnostic AUD remission. We hypothesize low persistency rates [1-4], but more persistency in those with more severe AUD (e.g. more AUD symptoms, higher alcohol consumption), psychiatric comorbidity and higher vulnerability (e.g. childhood abuse, negative life events). Finally, we expect that remitted cases show a 3-year decrease in drinking levels, but that more than one-quarter of them still has a risky drinking pattern. As validity of DSM-IV AUDs has been seriously criticized [26-32] regarding content and severity of criteria [26], presence of diagnostic orphans [27;28] and low validity of the alcohol abuse diagnosis [29-32], this paper uses DSM-5 AUD [33], which addressed most of these problems.

METHODS

Data were derived from two waves of NEMESIS-2 [34], a prospective epidemiologic survey in the general Dutch population. Baseline data (T_0) were collected in November 2007-July 2009. A multistage, stratified, random sampling procedure of households was applied with one respondent (aged 18-64), selected randomly from each household [34], resulting in a total sample of 6,646 adults (response: 65.1%). The 3-year follow-up wave (T_1) included 5,303 adults (response: 80.4%). Those who met criteria for DSM-5 AUD at T_0 (n = 198) were selected for the current study, of whom 155 (78.3% of T_0) were re-interviewed at T_1. No significant associations were found between baseline 12-month DSM-IV mental disorders and attrition [35].

The Composite International Diagnostic Interview (CIDI) version 3.0 was used at both waves to determine drinking patterns and DSM-IV mental disorder diagnoses. The CIDI is a fully structured, lay administered, interview developed by the World Health Organization (WHO), which is used worldwide. Clinical reappraisal interviews showed that it has generally good validity [36].

Persistency of alcohol use disorder

DSM-IV alcohol abuse and dependence symptoms were assessed with the CIDI, which also assessed craving: "Did you ever experience a time when you often had such a strong desire to drink that you couldn't stop yourself from taking a drink or found it difficult to think of anything else?". DSM-5 AUD symptoms include 3 of the 4 DSM-IV alcohol abuse criteria (without legal problems), all 7 DSM-IV alcohol dependence criteria and a new criterion covering craving [33]. DSM-5 AUD is diagnosed when ≥ 2 out of these 11 symptoms are present. Moreover, three severity levels are distinguished: mild (2-3 symptoms), moderate (4-5 symptoms) and severe (≥ 6 symptoms) [33]. All DSM-5 AUD symptoms were assessed using the CIDI 3.0. However, this instrument does not assess the DSM-5 clustering criterion (≥ 2 symptoms in the same 12-month period). Therefore, a symptom count was used to construct the diagnosis [37;38] and associated

severity levels. Persistency of AUD was defined as ≥ 2 DSM-5 AUD symptoms in the past 12 months at both T_0 and T_1.

Predictors of persistency

All predictors were recorded at T_0 except parental psychiatric history, which was assessed at T_1.

Sociodemographics included gender, age, low educational level (primary, basic vocational or lower secondary education), living without a partner, not having children at home, being unemployed, not having enough income to live on and living in an urban area.

AUD and drinking characteristics included the number of 12-month DSM-5 AUD symptoms, mean impairment in four areas of role functioning due to AUD (assessed with the Sheehan Disability Scale [39]), age of AUD onset, number of years that AUD was present (duration) and usual number of weekly drinks (see below).

Psychiatric comorbidity included 12-month mood disorder (major depression, dysthymia, bipolar disorder), anxiety disorder (panic disorder, agoraphobia, social phobia, specific phobia, generalized anxiety disorder), drug use disorder (drug abuse or dependence), and antisocial personality disorder.

Vulnerability factors were: smoking in the four weeks prior to the interview, lifetime parental history of depression/anxiety or of alcohol/drug addiction, mean number of 12-month negative life events (0-10) [40], having experienced psychological or physical abuse (more than once) or sexual abuse (once or more) before age 16, any 12-month service utilization and presence of a chronic somatic disease treated by a medical doctor in the previous 12 months.

Change in alcohol consumption

Mean number of weekly drinks at T_0 and T_1 were computed by multiplying answers to two questions: "In the past 12 months, how often did you usually have at least one drink – every day, nearly every day, 3-4 days a week, 1-2 days a week, 1-3 days a month, or less than once a month?" and "On the days you drank in the past 12 months, about how many drinks did you usually have per day?". Next, three variables regarding 3-year change in alcohol consumption were calculated: mean difference in number of weekly drinks (continuous), decrease in weekly alcohol consumption between T_0 and T_1 (yes/no) and increase in weekly alcohol consumption between T_0 and T_1 (yes/no).

A categorical variable representing three T_1 drinking categories was constructed: low-risk drinking (≤ 7/14 drinks weekly for women/men), moderate-risk drinking (8-14/15-21 drinks weekly for women/men) and high-risk drinking (> 14/21 drinks weekly for women/men). Additionally, a variable representing severe excessive alcohol consumption at T_1 was constructed including high-risk drinkers who also reported at least three 5+ drinking days a week [37].

Statistical analyses

First, the AUD persistency rate was established, as well as the prevalence rates and means of possible baseline predictors of 3-year AUD persistency. Secondly, these predictors were examined with univariable logistic regression analyses resulting in odds ratios (ORs) with 95% confidence intervals (CI). Thirdly, all predictors significant at $p < 0.10$ in univariable analyses were entered into a multivariable regression model to test them in relation to each other. McFadden's pseudo R^2 was computed for the multivariable model. Finally, the association between AUD persistency and alcohol consumption was examined while adjusting for gender and age.

Some predictors had missing data (six variables with two missing values and one with 24 missing values) and there was attrition of 43 respondents (21.7% of T_0) between T_0 and T_1. As complete case analyses may introduce bias, missing values were imputed using multiple imputation by chained equations. All predictor and outcome variables and some additional variables associated with attrition were used for the imputation. Using 800 imputation cycles, we imputed 20 datasets [41].

Analyses were performed using Stata version 12.1 [42]. All logistic regression models were adjusted for the number of days between respondents' T_0 and T_1 interview. The data were weighted to correct for baseline differences in response rates in subpopulations and in the probability of selection of respondents within households.

RESULTS

Sample description

Sample characteristics are portrayed in Table 4.1. On average, people with 12-month AUD at T_0 reported 3.3 AUD symptoms. Particularly, 69.3% had a mild, 17.3% a moderate and 13.4% a severe AUD. Functional disability due to AUD was fairly low, 1.2 on a scale from 0 to 10. Mean age of AUD onset was 21.3 and AUD duration was, on average, 10.4 years. Mean number of weekly drinks was 21.7.

Univariable predictors of persistency

Of the complete cases with baseline AUD (n = 155), 40 respondents still fulfilled the criteria of the disorder in the 12 months prior to T_1, corresponding with a weighted persistency rate of 30.9%. The imputed persistency rate was 29.5% (95% CI = 20.0; 39.0). Results of imputed data analyses showed that, on average, people with persistent AUD reported 4.2 AUD symptoms at T_1 and 57.2% of them had mild, 17.8% moderate and 24.9% severe AUD. Female gender, low educational level, living without a partner and not having children at home predicted persistency. Compared to the youngest (18-24), the older (25-34 and 35-44) age categories were at lower risk of AUD persistency. Also, persistency risk increased with more 12-month DSM-5 AUD symptoms, AUD disability and weekly drinks. In contrast, a longer AUD duration

Table 4.1. Baseline predictors of 3-year persistency of DSM-5 alcohol use disorder (AUD) in weighted column percentages or weighted means and weighted odds ratios (ORs) with 95% confidence intervals (95% CI) in people with baseline AUD (n = 198).

	Total	No persistency	Persistency	AUD persistency univariable analyses		AUD persistency multivariable analyses	
	% / mean	% / mean	% / mean	OR	(95% CI)	OR	(95% CI)
Sociodemographics (%)							
Gender: male	70.1	76.6	54.3	0.36*	(0.15; 0.86)	0.47	(0.11; 1.96)
Age (years)							
18-24 (ref)	28.0	16.7	54.9	1.00	-	1.00	-
25-34	28.2	36.8	7.7	0.06**	(0.01; 0.35)	0.05*	(0.00; 0.49)
35-44	21.6	25.7	11.8	0.14**	(0.04; 0.57)	0.14*	(0.02; 0.79)
45-64	22.2	20.8	25.6	0.37+	(0.12; 1.19)	0.36	(0.06; 2.16)
Low educational level	31.5	23.5	50.3	3.22*	(1.06; 9.78)	1.70	(0.30; 9.54)
Living without a partner	62.6	55.9	78.6	2.89*	(1.14; 7.30)	0.72	(0.16; 3.17)
No children at home	76.4	70.4	90.6	4.40*	(1.17; 16.46)	1.93	(0.39; 9.44)
Unemployed	21.2	18.1	28.3	1.64	(0.51; 5.29)	-	-
Not having enough income to live on	14.4	10.7	23.4	2.71	(0.76; 9.60)	-	-
Urbanization: urban	71.0	71.0	71.0	1.04	(0.37; 2.91)	-	-
Characteristics of AUD and drinking (mean)							
DSM-5 12-month AUD symptom count (2-11)	3.3	2.8	4.5	1.55***	(1.21; 1.99)	1.37	(0.87; 2.15)
Disability due to AUD (0-10)	1.2	1.0	1.9	1.38*	(1.06; 1.80)	0.82	(0.45; 1.48)
Onset of AUD	21.3	21.3	21.3	1.00	(0.95; 1.05)	-	-
Duration of AUD	10.4	12.2	6.4	0.92**	(0.86; 0.97)	0.95	(0.90; 1.02)
Number of weekly drinks	21.7	17.9	30.9	1.03**	(1.01; 1.05)	1.03*	(1.00; 1.07)

Table 4.1 continues on the next page.

Table 4.1. *Continued.*

	Total	No persistency	Persistency	AUD persistency univariable analyses		AUD persistency multivariable analyses	
	% / mean	% / mean	% / mean	OR	(95% CI)	OR	(95% CI)
Psychiatric comorbidity (%)							
12-month mood disorder	14.6	9.7	26.4	3.04+	(0.93; 9.92)	1.61	(0.22; 12.03)
12-month anxiety disorder	27.4	20.1	45.0	3.19*	(1.02; 9.97)	4.56*	(1.04; 20.06)
12-month drug use disorder	11.9	11.4	13.0	1.14	(0.21; 6.12)	-	-
Antisocial personality disorder	12.0	7.7	22.1	3.97+	(0.89; 17.68)	0.63	(0.06; 6.08)
Other vulnerability factors							
Smoking (%)	60.4	57.4	67.2	1.51	(0.62; 3.68)	-	-
Parental history of depression/anxiety (%)	38.1	36.3	42.4	1.22	(0.48; 3.11)	-	-
Parental history of alcohol/drug addiction (%)	22.6	22.9	21.9	0.94	(0.32; 2.80)	-	-
Mean number of negative life events (0-10)	1.3	1.1	1.9	1.35*	(1.05; 1.74)	0.91	(0.65; 1.27)
Childhood psychological abuse (%)	31.7	33.7	26.7	0.75	(0.28; 2.03)	-	-
Childhood physical abuse (%)	13.6	14.8	11.0	0.70	(0.16; 3.05)	-	-
Childhood sexual abuse (%)	9.4	9.3	9.4	0.96	(0.12; 7.60)	-	-
Any 12-month service utilization (%)	20.7	19.3	24.1	1.30	(0.39; 4.26)	-	-
Chronic somatic disease (%)	28.3	29.8	24.4	0.83	(0.26; 2.62)	-	-

Note. – Not calculated; + $p < 0.10$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. All predictors that had $p < 0.10$ in the univariable analyses were included in the multivariable analyses.

decreased this risk. Comorbid anxiety disorder and a higher number of negative life events predicted persistency.

Multivariable predictors of persistency

All predictors significant at $p < 0.10$ in the univariable analyses were included in the multivariable analyses. Compared to the youngest age group, the older (25-34 and 35-44) age categories were still at decreased risk of AUD persistency. Furthermore, a higher number of weekly drinks increased the risk of AUD persistency. The presence of a comorbid anxiety disorder increased this risk almost fivefold. Notably, the number of 12-month DSM-5 AUD symptoms was no longer associated significantly with persistency. The pseudo R^2 of the multivariable model was 25.2%.

Alcohol consumption and AUD persistency

Of all remitted persons, 61% showed a decrease and 24% an increase in the number of weekly drinks (Table 4.2) resulting in a mean reduction of 6 drinks per week between T_0 and T_1. In comparison, 51% of the people with a persistent AUD showed a decrease and 43% an increase in the number of weekly drinks, with an overall increase of 10 drinks per week.

Table 4.2. Three-year change in alcohol use and follow-up (T_1) alcohol use by persistency of DSM-5 alcohol use disorder (AUD) in weighted column percentages or weighted means and weighted odds ratios (ORs) with 95% confidence intervals (95% CI) in people with baseline AUD (n = 198).

	Total	No persistency	Persistency	AUD persistency	
	%/mean	%/mean	%/mean	OR	(95% CI)
3-year change in alcohol use					
Mean difference in number of weekly drinks	-1.0	-5.5	9.6	1.04*	(1.01; 1.06)
Decrease in number of weekly drinks (%)	58.2	61.1	51.1	0.56	(0.20; 1.56)
Increase in number of weekly drinks (%)	29.8	24.0	43.4	2.63	(0.90; 7.62)
T_1 alcohol use					
Mean number of weekly drinks	20.6	12.4	40.5	1.07**	(1.03; 1.12)
Amount of drinking (%)					
Low-risk drinking	51.3	64.2	20.3	1.00	-
Moderate-risk drinking	22.0	20.3	26.4	4.48*	(1.22; 16.40)
High-risk drinking	26.6	15.5	53.2	14.69***	(3.92; 54.99)
Excessive alcohol consumption (%)	15.7	7.7	34.9	10.66***	(2.98; 38.17)

Note. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Low-risk drinking: ≤ 7/14 drinks weekly for women/men; Moderate-risk drinking: 8-14/15-21 drinks weekly for women/men; High-risk drinking: > 14/21 drinks weekly for women/men; Excessive alcohol consumption: high-risk drinking *and* at least three 5+ drinking days a week. ORs were adjusted for age and gender.

On average, remitted individuals drank moderately, as shown by both the mean number of weekly drinks (12) and the proportion of low-risk drinking (64.2%). Low-risk drinkers can be divided further into a small group with abstention (no alcohol consumed: 9.2%) and a much larger group with low-risk drinking (≤ 7/14 drinks weekly for women/men: 55.0%). Nonetheless, 35.8% (95% CI = 22.4; 49.2) of the remitted individuals still drank considerably. Specifically, 20% drank at moderate risk, 16% at high risk and 8% met our criteria of excessive alcohol consumption, as they also had at least three 5+ drinking days per week. However, the group with persistent AUD drank much more: on average 41 drinks per week and 26% drank at moderate-risk, 53% at high-risk and 35% met criteria for excessive alcohol consumption.

DISCUSSION

Key findings

The 3-year AUD persistency rate was 29.5%, confirming the relatively low persistency rates in previous epidemiological research (e.g. [1-4]) with the new DSM-5 definition. Factors that could help to identify people at risk of AUD persistency were: younger age, a higher number of weekly drinks and comorbid anxiety disorder. Furthermore, 36% remitted individuals still drank considerably (> 7/14 drinks weekly for women/men), which puts them at risk of physical and mental harm related to excessive alcohol consumption [11-14].

Limitations

As alcohol consumption and AUD diagnosis were based on self-report, recall bias might be an issue. For example, regarding alcohol consumption, people may have difficulty remembering the amounts and frequencies in an average week which may have resulted in a biased estimate, most probably an underestimation of alcohol consumption [43].

In prospective studies, the validity of findings can be affected adversely by sample attrition [44-46]. However, in a previous report on NEMESIS-2, no such bias was found for DSM-IV mental disorders [35]. Additionally, as multiple imputation was used to deal with missing data, we assume that sample attrition has had little effect on the presented findings.

The DSM-5 clustering criterion (≥ 2 symptoms in the same 12-month period) was not assessed and therefore we used a symptom count to generate the AUD diagnosis [37;38]. This may have resulted in an overestimation of prevalence rates and an underestimation of AUD persistency. However, the bias is possibly limited because the presence of multiple symptoms has been associated with poor outcomes, regardless of 12-month clustering [47]. More importantly, the CIDI 3.0 was designed and validated with regard to DSM-IV AUDs [36] and not DSM-5 AUD. Although the criteria used in DSM-IV and DSM-5 are largely the same, the reliability of the DSM-5 AUD diagnosis

based on the CIDI 3.0 is unknown and could be lower than for DSM-IV, which may have resulted in a somewhat lower AUD persistency rate.

The number of subjects with DSM-5 AUD at baseline was limited, resulting in limited power in current analyses, thus precluding detection of smaller effects. Also, it was not possible to examine whether predictors of AUD persistency played a differential role in subgroups such as females, young adults or those with severe AUD.

Similar to previous studies [4;15], AUD persistency was regarded to be present if respondents reported 12-month AUD at both waves. Other longitudinal studies, including NESARC, used other definitions of persistency, such as the presence of at least one 12-month AUD symptom [20;21], including 12-month high-risk drinking [19] or the presence of AUD at any time between measurements [2;17]; or remission was divided in abstinent and non-abstinent remission [19]. Additionally, the follow-up period varied greatly among studies (range: 2-40 years [2-4,15,17,19-21,24]). These and other methodological differences hinder a direct comparison of findings.

Findings

Even though the 3-year persistency of DSM-5 AUD was quite low (30%), it was higher than persistency of DSM-IV alcohol abuse (15%) and dependence (25%) observed in a previous Dutch epidemiological study using a similar design and the same follow-up period [2]. These differences in persistency may be real differences, but may also reflect differences in CIDI 3.0 or DSM definitions. Nevertheless, confirming previous epidemiological research [48], it was observed in the present study that the vast majority of people with DSM-5 AUD had a mild form of AUD, which is likely to be associated with low levels of disability. This suggests, in combination with the low persistency rates, that an AUD diagnosis may not be clinically relevant for most people in the general population. It therefore seems imperative to use targeted interventions and to focus on those at risk of an unfavorable course.

Contrasting other studies [15;16], female gender predicted AUD persistency in the univariable analyses. Notably, a recent literature review observed that females in younger birth cohorts have a higher risk of AUDs than females in older birth cohorts [49]. Moreover, females have more severe AUD than males [50]. As we also observed that being in the youngest age group (18-24) predicted AUD persistency [16-18], this raises the question of whether or not risk of persistency may be strongest for females in the youngest age group. *Post-hoc* analyses confirmed this notion, as the persistency rate was much higher for young females (84%) than for older females (23%) or young (42%) or older males (17%). As young adults are obtaining an education or starting their career, alcohol problems at this age may seriously damage their prospect and thus attention for alcohol-related problems in young females seems desirable.

As hypothesized, more T_0 AUD symptoms [19], more AUD-related disability [3;15;20] and more weekly drinks [19] increased the risk of AUD persistency. Notably, only the number of weekly drinks remained a significant predictor in the multivariable model.

This may be due to limited statistical power, especially because only a small proportion of the subjects had a severe baseline AUD in terms of number of symptoms or AUD-related disability. However, it also suggests that number of weekly drinks predicts a severe AUD course independent of AUD severity. Future studies should thus consider both AUD severity and alcohol consumption to increase comprehension of the dynamics of AUDs [37]. Remarkably, in the univariable analyses, a longer duration of AUD decreased the risk of persistency. This finding seems counterintuitive, but is in accordance with previous observations [1]. Conceivably, it is caused by the high persistency rate in the youngest age group, for whom a long AUD duration is not yet possible.

Comorbid anxiety disorder was a powerful predictor of AUD persistency [51]. Anxiety disorders may predict AUD persistency because they are associated with more severe AUD or higher alcohol consumption. However, the stronger association between anxiety disorders and AUD persistency in the multivariable model contradicts this explanation. Alternatively, anxious people use alcohol to alleviate anxiety; i.e. as a form of self-medication [52;53], and therefore alcohol problems more often persist. A similar relation was expected with regard to mood disorders and AUD persistency [3;18;54], but although we observed more persistency in those with a mood disorder, this association was not statistically significant. Nevertheless, these findings indicate that people with an AUD should be monitored for symptoms of other mental disorders [55;56], as interventions targeting these symptoms could also prevent a more severe course of AUD.

The number of negative live events was the only vulnerability factor that increased persistency risk [22]. *Post-hoc* analyses showed that of the specific life events, only serious problems with someone important or financial difficulties increased this risk. Contrasting other studies [1;18;19;23], none of the other vulnerability factors (smoking, parental psychiatric history, abuse before age 16, service utilization and chronic somatic disease) were associated significantly with AUD persistency.

Drinking patterns of people with a remitted AUD changed in accordance with our expectations: remission was associated with decreased drinking levels, although only 9.2% abstained, indicating that a reduction in risk-drinking is more important for remission than abstinence per se [57]. Notably, 20% of those in diagnostic remission reported moderate-risk drinking and 16% high-risk drinking. As remitted individuals with continued excessive drinking patterns have an increased risk of relapse [12;13], it seems desirable that prevention of relapse focuses on this group. Unfortunately, the limited number of remitted individuals hindered us to identify characteristics associated with risk drinking while being in remission. Nevertheless, this finding suggests that no longer fulfilling DSM-5 AUD diagnostic criteria is necessary but not sufficient to define remission. Lastly, a significant part of those with a persisting AUD did not drink excessively. Although striking, this is in accordance with previous cross-sectional findings based on the same dataset [37]. As *post-hoc* analyses showed that the DSM-5 severity levels were gradually associated with the number of weekly drinks, it seems desirable to

take both DSM-5 severity and actual alcohol consumption into account when examining severity of the disorder.

Implications

In a large prospective population-based study fewer than one-third of the people with baseline AUD still had the disorder at 3-year follow-up. Interventions, including prevention strategies [58], should therefore pay extra attention to those at highest risk of persistency, namely younger people, and especially young women, with AUD and people with a comorbid anxiety disorder [10;52]. Furthermore, the number of weekly drinks was a predictor of a persistent course regardless of the number of AUD symptoms or AUD-related disability and could thus also be used to identify people at risk of persistency. Finally, it should be noted that people in recent diagnostic remission from AUD may still drink considerably with continued health-related risks and an increased risk of relapse. To help improve targeted relapse prevention, future studies should examine predictors of excessive drinking after diagnostic remission.

REFERENCES

1. Dawson D. A., Grant B. F., Stinson F. S., Chou P. S., Huang B., Ruan W. J. Recovery from DSM-IV alcohol dependence: United States, 2001-2002. *Alcohol Res Health* 2006; **29**: 131-42.
2. de Bruijn C., van den Brink W., de Graaf R., Vollebergh W. The three year course of alcohol use disorders in the general population: DSM-IV, ICD-10 and the Craving Withdrawal Model. *Addiction* 2006; **101**: 385-92.
3. Copeland W. E., Angold A., Shanahan L., Dreyfuss J., Dlamini I., Costello E. J. Predicting persistent alcohol problems: a prospective analysis from the Great Smoky Mountain Study. *Psychol Med* 2012; **42**: 1925-35.
4. Vergés A., Jackson K. M., Bucholz K. K., Grant J. D., Trull T. J., Wood P. K. *et al.* Deconstructing the age-prevalence curve of alcohol dependence: Why 'maturing out' is only a small piece of the puzzle. *J Abnorm Psychol* 2012; **121**: 511-23.
5. Schuckit M. A. Alcohol-use disorders. *Lancet* 2009; **373**: 492-501.
6. Rehm J., Mathers C., Popova S., Thavorncharoensap M., Teerawattananon Y., Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; **373**: 2223-33.
7. Thavorncharoensap M., Teerawattananon Y., Yothasamut J., Lertpitakpong C., Chaikledkaew U. The economic impact of alcohol consumption: A systematic review. *Subst Abuse Treat Prev Policy* 2009; **4**.
8. Room R., Babor T., Rehm J. Alcohol and public health. *Lancet* 2005; **365**: 519-30.
9. Volkow N. D., Li T. K. Drugs and alcohol: Treating and preventing abuse, addiction, and their medical consequences. In: Tsuang M. T., Stone W. S., Lyons M. J., editors. *Recognition and prevention of major mental and substance use disorders*. Arlington, VA US: American Psychiatric Publishing, Inc.; 2007. p. 263-96.
10. Miller N. S., Gold M. S. Dual diagnoses: psychiatric syndromes in alcoholism and drug addiction. *Am Fam Physician* 1991; **43**: 2071-6.
11. Rehm J., Baliunas D., Borges G. L. G., Graham K., Irving H., Kehoe T. *et al.* The relation between different dimensions of

alcohol consumption and burden of disease: An overview. *Addiction* 2010; **105**: 817-43.

12. Dawson D. A., Goldstein R. B., Grant B. F. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: A 3-year follow-up. *Alcohol Clin Exp Res* 2007; **31**: 2036-45.
13. Moos R. H., Moos B. S. Rates and predictors of relapse after natural and treated remission from alcohol use disorders. *Addiction* 2006; **101**: 212-22.
14. World Health Organization. *International guide for monitoring alcohol consumption and related harm*. Geneva: World Health Organization (WHO); 2000.
15. Boschloo L., Vogelzangs N., van den Brink W., Smit J. H., Beekman A. T. F., Penninx B. W. J. H. Predictors of the 2-year recurrence and persistence of alcohol dependence. *Addiction* 2012; **107**: 1639-40.
16. Lopez-Quintero C., Hasin D. S., de los Cobos J. P., Pines A., Wang S., Grant B. F. *et al.* Probability and predictors of remission from lifetime nicotine, alcohol, cannabis or cocaine dependence: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addiction* 2011; **106**: 657-69.
17. Grant J. D., Vergés A., Jackson K. M., Trull T. J., Sher K. J., Bucholz K. K. Age and ethnic differences in the onset, persistence and recurrence of alcohol use disorder. *Addiction* 2012; **107**: 756-65.
18. Pirkola S. P., Poikolainen K., Lönnqvist J. K. Currently active and remitted alcohol dependence in a nationwide adult general population - Results from the Finnish Health 2000 Study. *Alcohol Alcohol* 2006; **41**: 315-20.
19. Dawson D. A., Goldstein R. B., Ruan W. J., Grant B. F. Correlates of recovery from alcohol dependence: A prospective study over a 3-year follow-up interval. *Alcohol Clin Exp Res* 2012; **36**: 1268-77.
20. Penick E. C., Knop J., Nickel E. J., Jensen P., Manzardo A. M., Lykke-Mortensen E. *et al.* Do premorbid predictors of alcohol dependence also predict the failure to recover from alcoholism? *J Stud Alcohol Drugs* 2010; **71**: 685-94.
21. Zimmermann P., Wittchen H. U., Höfler M., Pfister H., Kessler R. C., Lieb R. Primary anxiety disorders and the development of subsequent alcohol use disorders: A 4-year community study of adolescents and young adults. *Psychol Med* 2003; **33**: 1211-22.
22. Dawson D. A., Grant B. F., Stinson F. S., Chou P. S. Maturing Out of Alcohol Dependence: The Impact of Transitional Life Events. *J Stud Alcohol* 2006; **67**: 195-203.
23. Cohen E., Feinn R., Arias A., Kranzler H. R. Alcohol treatment utilization: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Depend* 2007; **86**: 214-21.
24. Edens E. L., Glowinski A. L., Grazier K. L., Bucholz K. K. The 14-year course of alcoholism in a community sample: Do men and women differ? *Drug Alcohol Depend* 2008; **93**: 1-11.
25. Dawson D. A., Stinson F. S., Chou S. P., Grant B. F. Three-year changes in adult risk drinking behavior in relation to the course of alcohol-use disorders. *J Stud Alcohol Drugs* 2008; **69**: 866-77.
26. Saha T. D., Chou S. P., Grant B. F. Toward an alcohol use disorder continuum using item response theory: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychol Med* 2006; **36**: 931-41.
27. Harford T. C., Yi H. Y., Grant B. F. The five-year diagnostic utility of 'diagnostic orphans' for alcohol use disorders in a national sample of young adults. *J Stud Alcohol Drugs* 2010; **71**: 410-7.
28. Hasin D., Paykin A. Dependence symptoms but no diagnosis: Diagnostic 'orphans' in a community sample. *Drug Alcohol Depend* 1998; **50**: 19-26.
29. Hasin D. S., Van Rossem R., McCloud S., Endicott J. Differentiating DSM-IV alcohol dependence and abuse by course: Community heavy drinkers. *J Subst Abuse* 1997; **9**: 127-35.

30. Hasin D., Van Rossem R., McCloud S., Endicott J. Alcohol dependence and abuse diagnoses: Validity in community sample heavy drinkers. *Alcohol Clin Exp Res* 1997; **21**: 213-9.
31. Schuckit M. A., Danko G. P., Smith T. L., Bierut L. J., Bucholz K. K., Edenberg H. J. *et al.* The prognostic implications of DSM-IV abuse criteria in drinking adolescents. *Drug Alcohol Depend* 2008; **97**: 94-104.
32. Schuckit M. A., Smith T. L., Danko G. P., Bucholz K. K., Reich T. Five-year clinical course associated with DSM-IV alcohol abuse or dependence in a large group of men and women. *Am J Psychiatry* 2001; **158**: 1084-90.
33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Washington, DC: American Psychiatric Association (APA); 2013.
34. de Graaf R., ten Have M., van Dorsselaer S. The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. *Int J Methods Psychiatr Res* 2010; **19**: 125-41.
35. de Graaf R., van Dorsselaer S., Tuithof M., ten Have M. Sociodemographic and psychiatric predictors of attrition in the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). *Compr Psychiatry* 2013; **54**: 1131-9.
36. Haro J. M., Arbabzadeh-Bouchez S., Brugha T. S., De Girolamo G., Guyer M. E., Jin R. *et al.* Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. *Int J Methods Psychiatr Res* 2006; **15**: 167-80.
37. Tuithof M., ten Have M., van den Brink W., Vollebergh W., de Graaf R. The relationship between excessive alcohol consumption and alcohol use disorders according to DSM-IV and DSM-5. *Alcohol Clin Exp Res* 2014; **38**: 249-56.
38. Mewton L., Slade T., Teesson M. An Evaluation of the Proposed DSM-5 Cannabis Use Disorder Criteria Using Australian National Survey Data. *J Stud Alcohol Drugs* 2013; **74**: 614-21.
39. Leon A. C., Olfson M., Portera L., Farber L., Sheehan D.V. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med* 1997; **27**: 93-105.
40. Brugha T., Bebbington P., Tennant C., Hurry J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med* 1985; **15**: 189-94.
41. Sterne J. A., White I. R., Carlin J. B., Spratt M., Royston P., Kenward M. G. *et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; **338**: b2393.
42. Statacorp. Stata Statistical Software: Release 12. College Station, Texas: Statacorp LP; 2011.
43. Stockwell T., Donath S., Cooper-Stanbury M., Chikritzhs T., Catalano P., Mateo C. Under-reporting of alcohol consumption in household surveys: a comparison of quantity-frequency, graduated-frequency and recent recall. *Addiction* 2004; **99**: 1024-33.
44. Eaton W. W., Anthony J. C., Tepper S., Dryman A. Psychopathology and attrition in the epidemiologic catchment area surveys. *Am J Epidemiol* 1992; **135**: 1051-9.
45. Lamers F., Hoogendoorn A. W., Smit J. H., van Dyck R., Zitman F. G., Nolen W. A. *et al.* Sociodemographic and psychiatric determinants of attrition in the Netherlands Study of Depression and Anxiety (NESDA). *Compr Psychiatry* 2012; **53**: 63-70.
46. de Graaf R., Bijl R. V., Smit F., Ravelli A., Vollebergh W. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Am J Epidemiol* 2000; **152**: 1039-47.
47. Littlefield A. K., Vergés A., Sher K. J. Three (or more) alcohol-dependence symptoms

but not clustered in the same 12 months: Diagnostic orphans from a longitudinal perspective. *J Stud Alcohol Drugs* 2010; **71**: 864-9.

48. Merikangas K. R., McClair V. L. Epidemiology of substance use disorders. *Hum Genet* 2012; **131**: 779-89.
49. Keyes K. M., Li G., Hasin D. S. Birth cohort effects and gender differences in alcohol epidemiology: A review and synthesis. *Alcohol Clin Exp Res* 2011; **35**: 2101-12.
50. Keyes K. M., Martins S. S., Blanco C., Hasin D. S. Telescoping and gender differences in alcohol dependence: New evidence from two national surveys. *Am J Psychiatry* 2010; **167**: 969-76.
51. Bolton J., Cox B., Clara I., Sareen J. Use of Alcohol and Drugs to Self-Medicate Anxiety Disorders in a Nationally Representative Sample. *J Nerv Ment Dis* 2006; **194**: 818-25.
52. Kushner M. G., Abrams K., Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. *Clin Psychol Rev* 2000; **20**: 149-71.
53. Crum R. M., La F. L., Storr C. L., Green K. M., Stuart E. A., Alvanzo A.A. *et al.* Reports of drinking to self-medicate anxiety symptoms: longitudinal assessment for subgroups of individuals with alcohol dependence. *Depress Anxiety* 2013; **30**: 174-83.
54. Bolton J. M., Robinson J., Sareen J. Self-medication of mood disorders with alcohol and drugs in the National Epidemiologic Survey on Alcohol and Related Conditions. *J Affect Disord* 2009; **115**: 367-75.
55. Merikangas K. R., Angst J., Eaton W., Canino G. Comorbidity and boundaries of affective disorders with anxiety disorders and substance misuse: Results of an international task force. *Br J Psychiatry* 1996; **168**: 58-67.
56. Kessler R. C., Price R. H. Primary prevention of secondary disorders: A proposal and agenda. *Am J Community Psychol* 1993; **21**: 607-33.
57. Gastfriend D. R., Garbutt J. C., Pettinati H. M., Forman R. F. Reduction in heavy drinking as a treatment outcome in alcohol dependence. *J Subst Abuse Treat* 2007; **33**: 71-80.
58. Foxcroft D. R., Ireland D., Lister-Sharp D. J., Lowe G., Breen R. Longer-term primary prevention for alcohol misuse in young people: a systematic review. *Addiction* 2003; **98**: 397-411.

Chapter 5

Alcohol consumption and symptoms as predictors for relapse of DSM-5 alcohol use disorder

ABSTRACT

Background

Alcohol consumption levels and alcohol use disorder (AUD) symptoms may serve as easily quantifiable markers for AUD relapse after remission and might help prevention workers identify at-risk individuals. We investigated the predictive value of alcohol consumption and AUD symptoms on relapse.

Methods

Data are from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). We selected 506 people in ≥ 12-month DSM-5 AUD remission at baseline and assessed their status at 3-year follow-up. AUD symptoms and drinking patterns were assessed using the Composite International Diagnostic Interview 3.0. Time since remission was assessed retrospectively at baseline and ranged from 1 to 48 years. Predictors for relapse were examined using Cox regression analysis.

Results

Cumulative AUD relapse rate was 5.6% at 5 years, 9.1% at 10 years and 12.0% at 20 years. Relapse was predicted by both medium (15-28/22-42 drinks weekly for women/men) and high (≥ 29/43) past alcohol intake, ≥ 6 lifetime AUD symptoms, 'impaired control over use', and at-risk (≥ 8/15) current intake. The risk of relapse was especially high when medium or high past intake or ≥ 6 lifetime symptoms coincided with current at-risk drinking.

Conclusions

Only a minority of people in DSM-5 AUD remission relapsed, but the risk of relapse increased substantially with the presence of at least one of the risk factors. Moreover, at-risk current drinking coupled with other risk factors substantially increased the likelihood of relapse. Therefore, current drinking may provide an adequate reference point for relapse prevention.

Marlous Tuithof, Margreet ten Have, Wim van den Brink, Wilma Vollebergh, Ron de Graaf

Published in Drug and Alcohol Dependence (2014) 140: 85-91.

INTRODUCTION

Population-based studies suggest that approximately one in five people meet the criteria for an alcohol use disorder (AUD) in their lifetime [1-3]. The disorder usually presents itself in a mild form: approximately 70% go into remission within three years [4-6] and only a small minority of those in remission experience a relapse [5;7]. Even though relapse rates are low, the high personal and societal costs associated with chronic, recurrent AUD [8;9] warrant the need for relapse prevention measures. The small group at risk of recurrence should be distinguished from those with a high probability of sustained remission. Although information from longitudinal population-based research is limited, there are indications that alcohol consumption level and AUD symptoms could serve as easily quantifiable markers [10] which could help general practitioners and prevention workers to identify people at risk of relapse.

A 30-year prospective study among males observed that higher drinking frequency predicted relapse [11]. Longitudinal epidemiological studies have observed that past alcohol consumption predicted AUD incidence [12;13] and persistence [4;6], but to our knowledge, relapse after AUD remission has not been examined. There is also population-based evidence for the role of the number of AUD symptoms in predicting relapse [7], but the predictive value of specific AUD symptoms on relapse remains under-researched. Such information could be valuable because dependence symptoms and craving, rather than abuse symptoms, have been shown to be important predictors of AUD persistence in a longitudinal population-based study [14]. Specific symptoms may predict a severe course of AUD, including relapse. Moreover, as past alcohol intake and AUD symptoms are related [15], these aspects should be examined in relation to one another in order to determine their predictive value.

Furthermore, at-risk drinking during remission may present an additional risk [7]. Previous research has shown that roughly one-third of those in remission drink considerably (> 7 drinks weekly for women and > 14 drinks weekly for men [6;7]), and are at increased risk of relapse [7;15]. Moreover, at-risk drinking during remission may moderate the relationship between past alcohol intake and number or type of AUD symptoms and relapse. In particular, people with a high past alcohol intake or a high number of lifetime AUD symptoms who drink considerably during remission may have a particularly high risk of relapse.

This article aims to establish the predictive value of past alcohol intake, number and type of lifetime AUD symptoms and alcohol intake during remission on AUD relapse. Data are from a general population survey with 506 people in AUD remission in the 12-months before baseline and their 3-year follow-up. The study examines whether: (i) high past alcohol intake and a high number of lifetime AUD symptoms each predict AUD relapse; (ii) lifetime AUD symptom type predicts relapse independently of past alcohol intake; (iii) at-risk drinking during remission, i.e. current at-risk drinking, predicts relapse and moderates the relationship between lifetime AUD characteristics and relapse.

METHODS

Sample

Data were obtained from the first two waves of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2); a prospective epidemiologic survey in the general Dutch population. Baseline data (T_0) were collected between November 2007 and July 2009. A multistage, stratified, random sampling procedure of households was applied with one respondent randomly selected in each household [16]. This resulted in a total sample of 6,646 adults aged 18-64 (response: 65.1%) at baseline.

The Composite International Diagnostic Interview (CIDI) 3.0 was used at baseline (T_0) and 3-year follow-up (T_1) to identify drinking patterns and AUD diagnoses. Specifically, a lifetime version was administered at T_0 and a 3-year version at T_1. The CIDI is a fully structured, lay administered, internationally recognized interview developed by the WHO. Clinical reappraisal interviews indicate good validity [17].

Cohort

Using both retrospective and prospective data, we aimed to study the time to relapse for AUD in relation to associated risk factors among respondents in remission. To compile the study sample, respondents with a lifetime AUD diagnosis at T_0 (n = 706) were identified. Next, 198 individuals with a current AUD episode at T_0 and two individuals with invalid data on 'age of last AUD episode' were excluded. Of the remaining 506 subjects at risk of relapse, 421 (83.2% of T_0) were interviewed again at 3-year follow-up (T_1). Attrition was not associated with demographics (age and sex), past alcohol consumption level, number and type of lifetime AUD symptoms or current at-risk drinking (univariable analyses).

Assessments

Alcohol use disorder and symptoms. The CIDI 3.0 [18] assessed lifetime (T_0) and 3-year (T_1) presence of all separate DSM-5 AUD symptoms of alcohol abuse, dependence and craving [19]. The CIDI 3.0 assessed recency of the last episode of AUD retrospectively at T_0: respondents were asked at what age the previous AUD episode ended. The relapse age was assessed at T_1: respondents were asked at what age the first episode of AUD since T_0 began. The DSM-5 cluster criterion (≥ 2 symptoms in the same 12-month period) was not included in our diagnosis [6;20;21]. Based on DSM-5 severity levels, the lifetime number of symptoms was categorized as mild (2-3 symptoms), moderate (4-5 symptoms) or severe (≥ 6 symptoms) AUD.

Relapse. Relapse was deemed to have occurred if respondents reported ≥ 2 DSM-5 AUD symptoms between T_0 and T_1. Time to relapse was assessed using the age of recency reported at T_0 and the relapse age collected at T_1. For example, if a respondent was 48 at T_0 and the previous episode of AUD ended at age 43, the time in remission

was five years at baseline. If another episode of AUD is reported between T_0 and T_1 at age 49, time to relapse is 6 years.

Alcohol consumption. Past alcohol intake was calculated by multiplying answers to two questions: "Think about the years in your life when you drank most. During those years, how often did you usually have at least one drink: every day, nearly every day, 3-4 days a week, 1-2 days a week, 1-3 days a month, or less than once a month?" and "On the days you drank during those years, about how many drinks did you usually have per day?". Next, a categorical variable was constructed with three levels of past alcohol intake: low-risk drinking with ≤ 14/21 drinks weekly for women/men; medium-risk drinking with 15-28/22-42 drinks weekly for women/men; and high-risk drinking with ≥ 29/43 drinks weekly for women/men. The first cut-off point was drawn from internationally recognized low-risk drinking guidelines [22;23]; the second cut-off point doubled these numbers and was used to identify a high-risk group. Respondents answered two similar questions about alcohol intake in the past 12-months to assess current intake. Current at-risk drinking was set at ≥ 8/15 drinks weekly for women/men, a lower level than that used to assess past intake, in line with previous research [6;7].

Statistical analyses

AUD relapse (yes/no) during the 3-year follow-up period was the primary outcome variable. The Kaplan–Meier curve was used to estimate cumulative relapse rates, which are somewhat higher than unadjusted relapse rates, due to a correction for censored data [24]. For each year since remission, a relapse rate is calculated by dividing the number of people who relapsed by the number still at risk, thus without censored data for that point in time (i.e., data from those who already relapsed or those with a more recent remission). Cumulative relapse rates are calculated by multiplying the relapse rates reported up to that point. Thus, all respondents, including those not assessed at follow-up, were included in the analyses (n = 506).

After a check of the proportional hazards assumption (the shape of the survival function must be the same for all levels of a particular risk factor), both univariable and multivariable Cox regression analyses were performed to examine predictors for time to relapse, both separately and in relation to one another. This method corrects for censored data [24]. Finally, whether current at-risk drinking moderated the association between lifetime predictors (past alcohol intake, number of lifetime AUD symptoms, and significant symptom type) and AUD relapse was investigated using an additive model: additive interaction exists if the combined effect of lifetime characteristics and current at-risk drinking on AUD relapse is stronger than the sum of the separate effects. Additive interaction was tested by comparing the hazard ratio (HR) of lifetime characteristics and current at-risk drinking combined with the expected value in the event of no interaction: HR (AB) ≈ HR (A) + HR (B) - 1. If the expected HR is smaller

than the lower threshold of the 95% confidence interval for the HR of the combined effect, additive interaction is assumed [25-28].

Analyses were performed using Stata version 12.0 [29]. The data were weighted to correct for baseline differences in the response rates in different population groups and differences in the probability of respondent selection within households. As previous research suggests that age and sex affect relapse rates [7;30], all analyses were adjusted for age and sex.

RESULTS

Description of the sample

Table 5.1 shows age and sex of the total group and the separate alcohol use disorder characteristics. The majority of the 506 respondents in remission from DSM-5 AUD were male (76.0%) and had a mean age of 40 years (SE = 0.8). At baseline (T_0), time since remission ranged from 1 to 48 years with an average of 11 years (SE = 0.6) (not in table). Between T_0 and T_1, 46 respondents developed two or more DSM-5 AUD symptoms and were thus deemed to have relapsed. The estimated cumulative relapse rate was 1.4% at 1 year, 2.9% at 2 years, 5.6% at 5 years, 9.1% at 10 years and 12.0% at 20 years (Figure 5.1). Thereafter, remission appeared quite stable with a total cumulative relapse rate of 12.8% after 22 years.

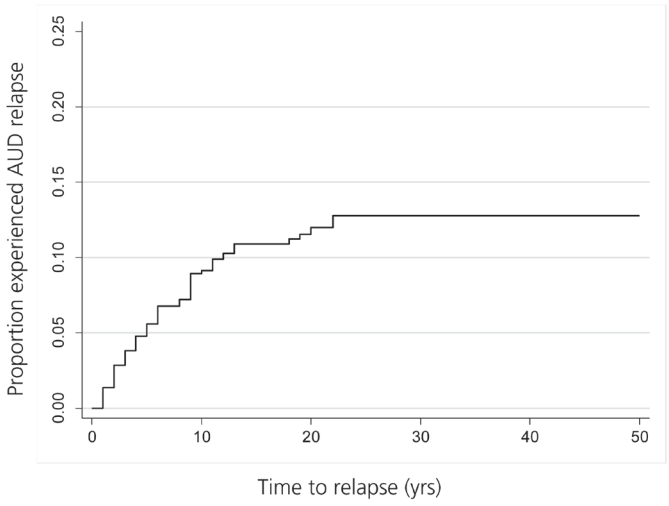


Figure 5.1. Kaplan-Meier curve of time to relapse of DSM-5 alcohol use disorder (AUD) in a cohort of respondents in remission from AUD at baseline (n = 506). The risk table presents the number of respondents at risk at the corresponding point in time.

Alcohol use disorder characteristics as predictors of relapse

Respondents had a mean past alcohol consumption level of approximately 50 drinks weekly (SE = 5.6) and reported on average 3.4 lifetime AUD symptoms (SE = 0.1). Notably, the correlation coefficient between past alcohol intake and number of lifetime symptoms was only 0.32. Table 5.1 shows that respondents were equally distributed across the three past alcohol intake categories. Moreover, the majority of the respondents (71.6%) reported lifetime mild AUD (2-3 symptoms), 14.0% reported moderate AUD (4-5 symptoms) and 14.4% reported severe AUD (≥ 6 symptoms). Univariable analyses showed that both medium (15-28/22-42 drinks weekly for women/men) and high (≥ 29/43) alcohol intake predicted relapse, as did lifetime severe AUD, but not lifetime moderate AUD. The multivariable model showed that high alcohol intake did not significantly predict relapse, but medium alcohol consumption and lifetime severe AUD did when adjusted for each others' effect. Based on these findings, two dichotomous variables were constructed for further analyses, for medium to high alcohol intake (yes/no) and presence of lifetime severe AUD (yes/no).

Prevalence was highest for the lifetime AUD symptoms 'larger quantities or longer than intended' and 'hazardous use', and lowest for 'important activities given up or reduced' and 'continued use despite physical or psychological harm' (Table 5.2). In the univariable analyses, risk of relapse was higher for the lifetime AUD symptoms 'impaired control over use', 'use despite social or interpersonal problems', and 'craving'. In the first multivariable model, which included symptoms with $p < 0.10$ in the univariable analyses, only 'impaired control over use' predicted relapse. The second multivariable model also included past alcohol intake and results showed that both 'impaired control over use' and past alcohol intake predicted relapse, independently of one another.

Current at-risk drinking

At baseline, 31.3% (n = 155) of the respondents reported current at-risk drinking, i.e. ≥ 8/15 drinks weekly for women/men during remission. The cumulative relapse rate of respondents with current at-risk drinking (25.3% after 20 years) was twice that of the overall cumulative relapse rate (12.0%). Current at-risk drinking predicted relapse in both univariable (HR = 4.74, 95% CI = 2.09; 10.78) and multivariable analyses [adjusted for significant lifetime characteristics: at least medium alcohol intake, lifetime severe AUD, and 'impaired control over use' (HR = 4.92, 95% CI = 2.16; 11.17)]. Moreover, moderation analyses demonstrated that current at-risk drinking exacerbated the effect of medium to high alcohol intake (HR = 9.72, 95% CI = 2.87; 32.94, cf 2.46) and lifetime severe AUD (HR = 25.84, 95% CI = 9.05; 73.76, cf 8.81) on the risk of relapse, but no significant moderation was observed with the lifetime AUD symptom 'impaired control over use' (Table 5.3).

Table 5.1. Past alcohol intake and number of lifetime AUD symptoms as predictors of AUD relapse (n = 46) in individuals with a DSM-5 AUD in diagnostic remission for at least 12 months at baseline (n = 506). Descriptives and results of Cox survival analyses in hazard ratios (HRs) with 95% confidence intervals (95% CI).

	Characteristics			Predicting relapse				
		Sex	Age		Univariable [b]		Multivariable [b, c]	
	%	% male	mean (SE)	Cumulative relapse rate [a]	HR	(95% CI)	HR	(95% CI)
Total sample	100.0	76.0	40.4 (0.8)	12.0	-	-	-	-
Past alcohol intake								
Low-risk drinking	32.5	78.8	38.3 (1.3)	4.6	1.00	-	1.00	-
Medium-risk drinking	33.7	77.3	40.0 (1.5)	16.3	3.90*	(1.20; 12.71)	3.86*	(1.19; 12.50)
High-risk drinking	33.8	72.0	42.9 (1.2)	14.2	3.77*	(1.26; 11.25)	2.84	(0.87; 9.27)
Number of lifetime AUD symptoms								
Mild: 2-3 symptoms	71.6	74.3	40.6 (1.0)	9.3	1.00	-	1.00	-
Moderate: 4-5 symptoms	14.0	76.7	38.3 (1.4)	10.9	1.15	(0.48; 2.77)	1.20	(0.45; 3.20)
Severe: ≥ 6 symptoms	14.4	83.9	41.5 (2.0)	27.9	3.35**	(1.38; 9.05)	3.35*	(1.09; 10.28)

Note. - Not calculated; * $p < 0.05$; ** $p < 0.01$. AUD: alcohol use disorder; Low-risk drinking: ≤ 14/21 drinks weekly for women/men; Medium-risk drinking: 15-28/22-42 drinks weekly for women/men; High-risk drinking: ≥ 29/43 drinks weekly for women/men.

[a] Cumulative relapse rate after 20 years calculated for each predictor; overall cumulative relapse rate after 20 years = 12.0%.

[b] Analyses were adjusted for sex and age.

[c] Predictors that had $p < 0.10$ in the univariable analyses were included.

Table 5.2. Lifetime AUD symptoms as predictors of AUD relapse (n = 46) in individuals with a DSM-5 AUD in remission for at least 12 months at baseline (n = 506). Results of Cox survival analyses in hazard ratios (HRs) with 95% confidence intervals (95% CI).

			Univariable [b]		Multivariable [b, c]		Multivariable [b, d]	
	%	Cumulative relapse rate [a]	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Lifetime AUD symptoms								
Larger quantities or longer than intended	81.3	13.8	2.86	(0.73; 11.20)	-	-	-	-
Impaired control over use	25.8	27.2	4.74***	(2.07; 10.86)	3.68***	(1.77; 7.64)	3.70***	(1.76; 7.77)
Great deal of time spent obtaining, using or recovering	20.6	21.6	2.04	(0.86; 4.82)	-	-	-	-
Failure to fulfill major role obligations	38.2	15.4	1.63	(0.79; 3.38)	-	-	-	-
Continued use despite social or interpersonal problems	16.9	21.0	2.34*	(1.01; 5.39)	1.44	(0.70; 2.97)	1.35	(0.65; 2.79)
Important activities given up or reduced	11.4	19.7	1.55	(0.66; 3.67)	-	-	-	-
Hazardous use	59.2	10.9	0.73	(0.37; 1.42)	-	-	-	-
Use despite physical or psychological harm	14.5	23.7	2.46+	(0.99; 6.12)	1.09	(0.45; 2.61)	1.22	(0.49; 3.05)
Tolerance	27.9	13.9	1.46	(0.66; 3.21)	-	-	-	-
Withdrawal	15.3	16.7	1.62	(0.74; 3.57)	-	-	-	-
Craving	25.4	22.6	2.79**	(1.35; 5.78)	1.62	(0.89; 2.93)	1.29	(0.67; 2.47)
Past medium-risk drinking	67.5	15.4	3.84*	(1.30; 11.33)	-	-	3.39*	(1.13; 10.16)

Note. - Not calculated; + $p < 0.10$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. AUD: alcohol use disorder. Past medium-risk drinking: ≥ 15/22 drinks weekly for women/men.
[a] Cumulative relapse rate after 20 years calculated for each predictor; overall cumulative relapse rate after 20 years = 12.0%.
[b] Analyses were adjusted for sex and age.
[c] All lifetime AUD symptoms that had $p < 0.10$ in the univariable analyses were included.
[d] All lifetime AUD symptoms that had $p < 0.10$ in the univariable analyses and past medium-risk drinking were included.

Table 5.3. Combined effects of lifetime characteristics and current at-risk drinking on relapse (n = 46) in individuals with a DSM-5 AUD in diagnostic remission for at least 12 months at baseline (n = 506). Results of Cox survival analyses in hazard ratios (HRs) with 95% confidence intervals (95% CI).

Combined effect of		Relapse [a]			
		HR	(95% CI)	p	Expected HR [b]
Past medium-risk drinking	Current at-risk drinking				
No	No	1.00	-	-	
Yes	No	1.98	(0.45; 8.68)	0.364	
No	Yes	1.48	(0.22; 9.96)	0.688	
Yes	Yes	**9.72**	**(2.87; 32.94)**	< 0.001	2.46
Lifetime severe AUD	Current at-risk drinking				
No	No	1.00	-	-	
Yes	No	4.33	(0.92; 20.44)	0.064	
No	Yes	5.48	(2.44; 12.28)	< 0.001	
Yes	Yes	**25.84**	**(9.05; 73.76)**	< 0.001	8.81
Impaired control over use	Current at-risk drinking				
No	No	1.00	-	-	
Yes	No	9.11	(2.31; 35.98)	0.002	
No	Yes	8.68	(2.58; 29.20)	0.001	
Yes	Yes	29.65	(9.80; 89.69)	< 0.001	16.79

Note. - Not calculated. In bold means significant at 0.05 for the combined effect. AUD: alcohol use disorder; Current at-risk drinking: ≥ 8/15 drinks weekly for women/men; Past medium-risk drinking: ≥ 15/22 drinks weekly for women/men; Lifetime severe AUD: ≥ 6 lifetime AUD symptoms.

[a] Analyses were adjusted for sex and age.

[b] Expected HR in the case of no interaction is the sum of the separate effects of the lifetime characteristic and current at-risk drinking. Additive interaction is assumed if the expected HR lies below the lower limits of the confidence intervals of the combined effect of the lifetime characteristic and current at-risk drinking.

DISCUSSION

Key findings

In this longitudinal population-based study, the cumulative relapse rate of DSM-5 AUD after 20 years was only 12%, with very few new cases of relapse. Past alcohol intake and number of lifetime symptoms were important predictors, each contributing to the risk of relapse, independently. Therefore, both characteristics could be used to target relapse prevention efforts. This was also true for the lifetime AUD symptom 'impaired control over use'. Special attention should be paid to reducing intake among people in remission: this was a strong independent predictor of relapse and current at-risk drinking exacerbated the effect of past alcohol consumption levels and number of lifetime AUD symptoms on the risk of relapse.

Limitations

When interpreting the findings, the following limitations should be taken into account. First, the DSM-5 clustering criterion (≥ 2 symptoms in the same 12-month period) was not included in our AUD diagnosis [6;20;21]. This may have resulted in some overestimation of the lifetime prevalence of AUD. However, this effect is likely to be small because multiple symptoms have been shown to be associated with poor outcomes, regardless of 12-month clustering [31]. Second, the CIDI 3.0 was designed and validated for the assessment of DSM-IV AUDs [17], not for DSM-5 AUD. Although the criteria used in DSM-IV and DSM-5 are very similar, reliability of the DSM-5 AUD diagnosis based on the CIDI 3.0 is unknown and could be lower than for DSM-IV, which may have resulted in a somewhat higher relapse rate. Third, in line with other population-based surveys, alcohol intake and AUD symptoms and AUD remission were assessed by self-report. Reports on such behavior may be influenced by social stigma. Moreover, people may have difficulties remembering which symptoms were present or the exact time since the last episode of AUD, particularly people in long-term remission. Such biases may have resulted in an underestimation of the predictive value of past drinking levels and lifetime AUD symptoms. Fourth, in prospective studies, the internal validity of findings may be affected by selective attrition [32-34]. Assuming that censoring is noninformative (independent of the study outcome – in this instance AUD relapse), Cox regression deals with censored data. In NEMESIS-2, attrition was not associated with DSM-IV mental disorders after adjusting for sociodemographic characteristics [35] and we observed no association between attrition and relapse predictors in the present study. Therefore, sample attrition is unlikely to have an important effect on our findings. Finally, the present study focused on easily quantifiable markers of AUD relapse. However, a broader set of risk factors, such as comorbid psychopathology and childhood maltreatment, is likely to be relevant for prediction of relapse and should be examined in future research.

Findings

This major longitudinal population-based study shows that only a small minority of people with lifetime AUD experience a relapse [5;7] - the cumulative relapse rate after 20 years was 12.0%. Comparison with previously observed relapse rates is difficult due to methodological differences. For example, a previous prospective general population study in the Netherlands [5] observed a 2-year relapse rate of DSM-IV alcohol abuse and alcohol dependence of 10.0% and 13.6%, respectively. Initially, this seems much higher than our cumulative 2-year relapse rate (2.9%). However, that study only included people in 12-month diagnostic remission [5], thus, no individuals in long-term remission, whereas risk of relapse decreases with time since remission [7]. *Post-hoc* analyses confirmed that the focus on individuals only recently in remission explains this discrepancy. Specifically, 41 participants in our study had a remission time of only 1 year at baseline and their relapse rate at 3-year follow-up was 14.8%, i.e. comparable to

the previous study in the Netherlands. Thus, taking into account time since remission has a major impact on the findings and is therefore an essential factor when examining predictors for relapse. Moreover, as this was the first population-based study, which assessed time to relapse, we could observe that the relapse was quite stable at a very low level after 20 years.

The weak correlation coefficient between past alcohol intake and number of lifetime AUD symptoms is in line with previous, cross-sectional, findings from NEMESIS-2. Specifically, limited overlap between excessive drinking and AUDs was observed, suggesting that these factors are indicative of discrete aspects of problematic alcohol use [21]. The current study observed that past alcohol intake and number of lifetime AUD symptoms both predicted relapse, independently of one another. General practitioners could use both aspects to identify people with lifetime AUD at-risk of relapse. In DSM-5, AUD severity is assessed on a scale based on the number of symptoms: mild (2-3 symptoms), moderate (4-5 symptoms) and severe (≥ 6 symptoms). Whereas there were no significant difference in relapse risk between those with mild and those with moderate AUD, the small group of people with severe AUD (14.4%) were at substantially higher risk of relapse. Even though prevention of relapse in the larger group with mild or moderate AUD could prevent more costs at societal level [36], targeting this smaller, but more severe group seems more efficient, given the strong association with relapse. The effect of past alcohol intake was somewhat difficult to ascertain as the risk of relapse was substantially increased in groups with past alcohol intake of just ≥ 15/22 drinks weekly for women/men, including two-thirds of those in AUD remission. This group is much too large for targeted prevention and therefore past alcohol consumption may be better used as a marker for relapse in combination with other risk factors.

Of the specific AUD symptoms, we found that 'impaired control over use' (lifetime prevalence: 25.8%) was the strongest predictor of relapse both in univariable analyses and when controlled for the presence of other significant symptoms and past alcohol intake. This specific AUD symptom has also been found to predict other associated phenomena, such as incidence of substance use disorders [37;38] and AUD persistence [14]. The present findings show that even when people with this symptom succeed in controlling their drinking and remit from AUD, risk of relapse remains high, i.e., more than a quarter of them relapsed within 20 years. In the CIDI 3.0, the exact wording of this symptom was: "Were there times when you tried to stop or cut down on your drinking and found that you were not able to do so?". Notably, this is somewhat stricter than the DSM-5 definition of the symptom (i.e., "persistent desire or unsuccessful efforts to cut down or control use") and also stricter than the definition of impaired control in the early models of alcoholism, which more generally referred to an "inability to control one's drinking" [39;40]. Even though the rather strict CIDI definition may have strengthened the role of impaired control in the prediction of relapse, the definition is concrete and can be easily and reliably assessed [17]. Moreover, the early models of

alcoholism already described loss of control as a core aspect of alcoholism and that perspective is supported by the current findings.

Regarding craving, findings in this population-based study only partly confirm previous clinical findings in which craving was identified as an important predictor for relapse [41]. Previous epidemiological research has led to skepticism with regard to the role of craving in the diagnosis of AUD. For example, Keyes at al. observed that with the addition of craving, few new cases were identified and only limited additional information regarding severity of the disorder was obtained [42]. Nevertheless, our findings suggest that lifetime craving might be of some value in identifying people at risk of relapse as more than one-fifth of the individuals with lifetime presence of craving relapsed within 20 years.

In line with previous research [7], we observed that at-risk drinking during remission increased the risk of relapse. This was also the case when adjusted for the effect of other significant lifetime predictors. As current drinking patterns can be easily identified, at-risk drinking may provide an adequate starting point for relapse prevention. Moreover, we observed that an accumulation of risk factors substantially increased the likelihood of relapse. Particularly, at-risk drinking during remission intensified the relationship between medium to high past alcohol intake and relapse, as well as that between lifetime severe AUD and relapse. This suggests that for people with those severe lifetime characteristics of AUD, special attention should be given to drinking habits during remission. Focus on abstinence or very low intake is advisable for this group.

Implications

Our findings suggest that lifetime AUD characteristics may help to detect individuals at risk of chronic, recurrent AUD. Those with higher past alcohol intake or more lifetime AUD symptoms, as well as those with 'impaired control over use' seem to have an increased risk of relapse. Careful monitoring and assistance for people with these characteristics may prevent relapse. In addition, special attention should be paid to drinking patterns during remission. Reduced-risk drinking is frequently used in web-based interventions [43;44] and clinical settings [45], but a focus on abstinence or very low intake seems preferable [7].

REFERENCES

1. de Graaf R., ten Have M., van Gool C., van Dorsselaer S. Prevalence of mental disorders and trends from 1996 to 2009. Results from the Netherlands mental health survey and incidence study-2. *Soc Psychiatry Psychiatr Epidemiol* 2012; **47**: 203-13.
2. Hasin D. S., Stinson F. S., Ogburn E., Grant B. F. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2007; **64**: 830-42.
3. Teesson M., Hall W., Slade T., Mills K., Grove R., Mewton L. *et al.* Prevalence and correlates of DSM-IV alcohol abuse and

dependence in Australia: Findings of the 2007 National Survey of Mental Health and Wellbeing. *Addiction* 2010; **105**: 2085-94.

4. Dawson D. A., Goldstein R. B., Ruan W. J., Grant B. F. Correlates of recovery from alcohol dependence: A prospective study over a 3-year follow-up interval. *Alcohol Clin Exp Res* 2012; **36**: 1268-77.
5. de Bruijn C., van den Brink W., de Graaf R., Vollebergh W. The three year course of alcohol use disorders in the general population: DSM-IV, ICD-10 and the Craving Withdrawal Model. *Addiction* 2006; **101**: 385-92.
6. Tuithof M., ten Have M., Van den Brink W., Vollebergh W., de Graaf R. Predicting persistency of DSM-5 alcohol use disorder and examining drinking patterns of recently remitted individuals: a prospective general population study. *Addiction* 2013; **108**: 2091-9.
7. Dawson D. A., Goldstein R. B., Grant B. F. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: A 3-year follow-up. *Alcohol Clin Exp Res* 2007; **31**: 2036-45.
8. Rehm J., Mathers C., Popova S., Thavorncharoensap M., Teerawattananon Y., Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; **373**: 2223-33.
9. Volkow N. D., Li T. K. Drugs and alcohol: Treating and preventing abuse, addiction, and their medical consequences. In: Tsuang M. T., Stone W. S., Lyons M. J., editors. *Recognition and prevention of major mental and substance use disorders*. Arlington, VA US: American Psychiatric Publishing, Inc.; 2007. p. 263-96.
10. Li T. K., Hewitt B. G., Grant B. F. Is there a future for quantifying drinking in the diagnosis, treatment, and prevention of alcohol use disorders? *Alcohol Alcohol* 2007; **42**: 57-63.
11. Trim R. S., Schuckit M. A., Smith T. L. Predictors of Initial and Sustained Remission from Alcohol Use Disorders: Findings from the 30-Year Follow-Up of the San Diego Prospective Study. *Alcohol Clin Exp Res* 2013; **37**: 1424-31.
12. Corrao G., Bagnardi V., Zambon A., La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med* 2004; **38**: 613-9.
13. Dawson D. A., Stinson F. S., Chou S. P., Grant B. F. Three-year changes in adult risk drinking behavior in relation to the course of alcohol-use disorders. *J Stud Alcohol Drugs* 2008; **69**: 866-77.
14. de Bruijn, C., Van den Brink W., de Graaf R., Vollebergh W. Alcohol abuse and dependence criteria as predictors of a chronic course of alcohol use disorders in the general population. *Alcohol Alcohol* 2005; **40**: 441-6.
15. Moos R. H., Moos B. S. Rates and predictors of relapse after natural and treated remission from alcohol use disorders. *Addiction* 2006; **101**: 212-22.
16. de Graaf R., ten Have M., van Dorsselaer S. The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. *Int J Methods Psychiatr Res* 2010; **19**: 125-41.
17. Haro J. M., Arbabzadeh-Bouchez S., Brugha T. S., De Girolamo G., Guyer M. E., Jin R. *et al.* Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. *Int J Methods Psychiatr Res* 2006; **15**: 167-80.
18. Kessler R. C., Ustun T. B. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res* 2004; **13**: 93-121.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Washington, DC: American Psychiatric Association (APA); 2013.
20. Mewton L., Slade T., Teesson M. An Evaluation of the Proposed DSM-5 Cannabis

Use Disorder Criteria Using Australian National Survey Data. *J Stud Alcohol Drugs* 2013; **74**: 614-21.

21. Tuithof M., ten Have M., van den Brink W., Vollebergh W., de Graaf R. The relationship between excessive alcohol consumption and alcohol use disorders according to DSM-IV and DSM-5. *Alcohol Clin Exp Res* 2014; **38**: 249-56.
22. Haynes J. C., Farrell M., Singleton N., Meltzer H., Araya R., Lewis G. *et al.* Alcohol consumption as a risk factor for anxiety and depression: Results from the longitudinal follow-up of the National Psychiatric Morbidity Survey. *Br J Psychiatry* 2005; **187**: 544-51.
23. British Medical Association. *Alcohol guidelines on sensible drinking.* London: British Medical Association (BMA); 1995.
24. Kleinbaum D. G., Klein M. *Survival Analyses. A self-learning text.* Second ed. New York: Springer; 2005.
25. Ahlbom A., Alfredsson L. Interaction: A word with two meanings creates confusion. *Eur J Epidemiol* 2005; **20**: 563-4.
26. Rothman K. J. *Epidemiology. An Introduction*. New York: Oxford University Press; 2002.
27. ten Have M., Vollebergh W., Bijl R., Ormel J. Combined effect of mental disorder and low social support on care service for mental health problems in the Dutch general population. *Psych Med* 2002; **32**: 311-23.
28. Tuithof M., ten Have M., van den Brink W., Vollebergh W., de Graaf R. The role of conduct disorder in the association between ADHD and alcohol use (disorder). Results from the Netherlands Mental Health Survey and Incidence Study-2. *Drug Alcohol Depend* 2012; **123**: 115-21.
29. Statacorp. Stata Statistical Software: Release 12. College Station, Texas: Statacorp LP; 2011.
30. Grant J. D., Vergés A., Jackson K. M., Trull T. J., Sher K. J., Bucholz K. K. Age and ethnic differences in the onset, persistence and recurrence of alcohol use disorder. *Addiction* 2012; **107**: 756-65.
31. Littlefield A. K., Vergés A., Sher K. J. Three (or more) alcohol-dependence symptoms but not clustered in the same 12 months: Diagnostic orphans from a longitudinal perspective. *J Stud Alcohol Drugs* 2010; **71**: 864-9.
32. Eaton W. W., Anthony J. C., Tepper S., Dryman A. Psychopathology and attrition in the epidemiologic catchment area surveys. *Am J Epidemiol* 1992; **135**: 1051-9.
33. de Graaf R., Bijl R. V., Smit F., Ravelli A., Vollebergh W. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Am J Epidemiol* 2000; **152**: 1039-47.
34. Lamers F., Hoogendoorn A.W., Smit J. H., van Dyck R., Zitman F. G., Nolen W. A. *et al.* Sociodemographic and psychiatric determinants of attrition in the Netherlands Study of Depression and Anxiety (NESDA). *Compr Psychiatry* 2012; **53**: 63-70.
35. de Graaf R., van Dorsselaer S., Tuithof M., ten Have M. Sociodemographic and psychiatric predictors of attrition in the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). *Compr Psychiatry* 2013; **54**: 1131-9.
36. Caetano R., Mills B., Pinsky I., Zaleski M., Laranjeira R. The distribution of alcohol consumption and the prevention paradox in Brazil. *Addiction* 2012; **107**: 60-8.
37. de Graaf R., Bijl R. V., Ravelli A., Smit F., Vollebergh W. Predictors of first incidence of DSM-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health Survey and Incidence Study. *Acta Psychiatr Scand* 2002; **106**: 303-13.
38. van der Pol P., Liebregts N., de Graaf R., Korf D. J., Van den Brink W., van Laar M. Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study. *Drug Alcohol Depend* 2013; **133**: 352-9.
39. Jellinek E. M. *The Disease Concept of Alcoholism*. New Brunswick: Hillhouse Press; 1960.

40. Edwards G., Gross M. M. Alcohol dependence: provisional description of a clinical syndrome. *Br Med J* 1976; **1**: 1058-61.
41. Oslin D. W., Cary M., Slaymaker V., Colleran C., Blow F. C. Daily ratings measures of alcohol craving during an inpatient stay define subtypes of alcohol addiction that predict subsequent risk for resumption of drinking. *Drug Alcohol Depend* 2009; **103**: 131-6.
42. Keyes K. M., Krueger R. F., Grant B. F., Hasin D. S. Alcohol craving and the dimensionality of alcohol disorders. *Psychol Med* 2011; **41**: 629-40.
43. Riper H., Spek V., Boon B., Conijn B., Kramer J., Martin-Abello K. *et al.* Effectiveness of E-self-help interventions for curbing adult problem drinking: a meta-analysis. *J Med Internet Res* 2011; **13**: e42.
44. White A., Kavanagh D., Stallman H., Klein B., Kay-Lambkin F., Proudfoot J. *et al.* Online alcohol interventions: a systematic review. *J Med Internet Res* 2010; **12**: e62.
45. van Amsterdam J., van den Brink W. Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. *J Psychopharmacol* 2013; **27**: 987-97.

Chapter 6

Treatment seeking for alcohol use disorders:

treatment gap or adequate self-selection?

ABSTRACT

Objective

To examine whether it is harmful that subjects with an alcohol use disorder (AUD) in the general population rarely seek treatment.

Method

Subjects with a 12-month DSM-5 AUD at baseline and 3-year follow-up data (n = 154) from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) were divided in three mutually exclusive groups: AUD subjects who used (1) only general treatment for mental health or alcohol/drugs problems; (2) specialized AUD treatment; and (3) no treatment. Treatment utilization covered a 4-year period. The Composite International Diagnostic Interview 3.0 assessed AUD and other psychiatric disorders.

Results

Four-year treatment rates were: 35.4% general treatment; 10.3% AUD treatment; 54.3% no treatment. Of the three groups, AUD treatment users showed the highest baseline and/or follow-up severity on AUD characteristics, comorbid psychopathology and mental functioning. Compared to non-treatment, general treatment users more often had a 12-month emotional disorder at follow-up, but they did not differ significantly in their AUD remission rate and functioning. Moreover, follow-up functioning of non-treatment users was similar to that of people in the general population without a lifetime diagnosis of AUD and of other psychopathology.

Conclusion

Despite low treatment rates, adequate treatment selection is suggested: the most severe AUD subjects use AUD treatment and non-treatment users generally have a favorable AUD course. Yet, minorities of non-treatment and general treatment users suffered from persistent AUD and may benefit from guidance to AUD treatment. In summary, the treatment gap seems smaller than often assumed, but there is a substantial need for increased AUD treatment participation.

Marlous Tuithof, Margreet ten Have, Wim van den Brink, Wilma Vollebergh, Ron de Graaf

Under review.

INTRODUCTION

For decades, concerns have been raised regarding the large treatment gap of alcohol use disorders (AUDs): the majority of the people who experience AUD do not enter AUD treatment (AUDTx) [1-3]. For example, two population-based surveys in the USA showed that only 8% of those with past-year AUD received AUDTx during that period [2]. These findings were recently extended by examination of the delay in treatment utilization. In the Netherlands, only 7% of those with lifetime alcohol abuse and only 37% of those with lifetime alcohol dependence eventually received AUDTx, with a median delay of 1 and 4 years after AUD onset, respectively [4]. Somewhat higher treatment rates but also longer delays are observed worldwide [5-7]. A long-term unmet need for treatment of AUDs may thus exist and improvement of treatment access has been suggested a public health priority [8-10].

However, others have questioned the magnitude of the treatment gap for AUD, because the prevalence of a disorder may not be sufficient to establish treatment need when its clinical significance and the natural course have not been determined [11-13]. Indeed, population-based research showed that AUDs, and especially alcohol abuse, are often mild and do not interfere strongly with daily activities [13-15]. Moreover, AUDs in the general population are associated with high spontaneous remission rates [16-19] and thus not all of those with an AUD diagnosis may actually need AUDTx. It is undesirable when severe AUD cases do not receive treatment, but when non-treatment (NonTx) users turn out to be mild AUD cases with a favorable course, their decision not to seek treatment may be justified and likely be cost-effective. Lastly, the treatment gap may be smaller than projected because people with AUD may receive general treatment for mental health or other addiction problems (GenTx) rather than AUDTx [2;20]. Although GenTx is not likely to focus on the AUD [21;22], it may be possible to achieve a favorable AUD outcome when any type of general treatment is received.

To guide the discussion on the treatment gap, four aspects should be considered. First, given the present context of limited resources, especially people with a severe disorder should enter AUDTx. Preferably, both severe clinical characteristics and high rates of alcohol consumption trigger AUDTx utilization, as both aspects are markers of a severe AUD course [15;16;18;23;24]. Previous research indeed showed that the first aspect, severe clinical characteristics in terms of alcohol dependence (vs. alcohol abuse) and severe impairment due to AUD, was associated with AUDTx utilization [2]. The second aspect, rate of alcohol consumption, was not yet examined in this regard and its impact on treatment utilization is therefore unknown. Second, people with AUD often receive GenTx rather than AUDTx [2]. Whether GenTx users are able to sufficiently cope with the AUD or whether the problems remain is unknown. Knowledge regarding how GenTx users are doing is lacking but this is essential to determine the magnitude of the treatment gap. Third, previous research revealed a substantial delay between AUD

onset and AUDTx entrance [4;5;7]. Therefore, a longitudinal perspective with regard to treatment use, thus not only past-year treatment but also treatment in the following years, is preferable to include delayed treatment seekers as well. Fourth, information on the clinical course of NonTx AUD subjects is crucial to better understand the magnitude of the treatment gap. Comparing their AUD status at follow-up with that of (different types of) treatment users is important but not sufficient: NonTx users might show a better AUD course than treatment users but may still be somewhat impaired. An additional comparison with people who never had an AUD or other psychopathology would therefore advance the interpretation of their functioning.

Data from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2) were used to study these four aspects. Four-year treatment utilization and associated baseline and follow-up characteristics (i.e. demographics, AUD characteristics, comorbid psychiatric disorders, functioning) were investigated for three groups: GenTx, AUDTx and NonTx. Specific attention was paid to the association between alcohol intake and treatment utilization and the follow-up clinical status and functioning of NonTx users.

METHOD

Study design

NEMESIS-2 is a psychiatric epidemiological cohort study of the Dutch general population. It is based on a multistage, stratified random sampling of households, with one respondent randomly selected in each household [25]. The study was approved by a medical ethics committee. After having been informed about the study aims, respondents provided written informed consent.

In the first wave (T_0), performed from November 2007 to July 2009, a total of 6,646 persons aged 18-64 were interviewed (response: 65.1%). This sample was nationally representative, although younger subjects were somewhat underrepresented [25]. The face-to-face interviews were mainly held at the respondent's home. All T_0 respondents were approached for follow-up (T_1), three years after T_0 from November 2010 to June 2012. Of this group, a total of 5,303 persons were interviewed again (response: 80.4%, with those deceased excluded). Attrition was not significantly associated with any of 12-month psychiatric disorders at baseline, after controlling for sociodemographics [26]. To compile the current study sample, those who met criteria for DSM-5 AUD at T_0 and participated in the 3-year follow-up assessment (T_1) were selected (n = 154).

Alcohol use disorder

The Composite International Diagnostic Interview (CIDI) 3.0 was used at both waves to identify AUD diagnoses. The CIDI 3.0 is a fully structured, lay administered, internationally recognized interview developed by the WHO [27]. Even though the CIDI

3.0 was designed and validated for DSM-IV AUDs [27;28], it assesses all DSM-5 AUD criteria: 3 of the 4 DSM-IV alcohol abuse criteria (except legal problems), all 7 DSM-IV alcohol dependence criteria, and craving [29]. DSM-5 AUD is diagnosed when ≥ 2 out of these 11 criteria are present. The DSM-5 cluster criterion (≥ 2 criteria in the same 12-month period) was not included in our AUD diagnosis [15;30;31].

Treatment

The focus was on treatment during the study period. This period was 4 years: 1 year before baseline to 3-year follow-up. Treatment was present when respondents reported past-year treatment at T_0 or treatment between T_0 and T_1. Three mutually exclusive groups were distinguished: GenTx only, AUDTx; and NonTx.

First, it was examined whether respondents had received general treatment (GenTx) including at least one contact made with a professional in the general medical care or mental health care system for emotional or alcohol/drugs problems. It was assessed with the question: "In the past 12 months (T_0)/since the last interview (T_1), did you visit any of the following professionals or institutions because of emotional or alcohol or drugs problems of your own?" [13]. Included were general medical professionals (general practitioners, company doctors, social workers, home care or district nurses, physiotherapists or haptonomists, medical specialists or other professionals working the general medical care sector) and mental health services (psychiatrists, psychologists, psychotherapists, part-time or full-time psychiatric treatment).

Next, it was examined whether respondents reported AUD treatment (AUDTx) in the CIDI 3.0 AUD section. That is, as in other research (e.g. [5]), respondents were asked whether they received professional treatment or whether they talked to a medical doctor or other professional about their alcohol problems in the past 12 months (T_0)/since last interview (T_1). Then, GenTx only was coded absent for those who also reported AUDTx.

Lastly, respondents who reported neither GenTx nor AUDTx during the study period were labelled NonTx users.

Baseline and follow-up characteristics

Demographics were collected at the first wave. All other characteristics were assessed at both waves.

Demographics. Gender, age, educational level (primary, basic vocational or lower secondary education vs. higher education), partner status, employment, having enough income to live on or not.

Characteristics of AUD and drinking. All characteristics of AUD and drinking were assessed with the CIDI 3.0. Following the severity levels defined by DSM-5 [29], the number of 12-month AUD criteria were divided in categories: no disorder (0-1 criterion); mild AUD (2-3 criteria); and moderate/severe AUD (≥ 4 criteria).

Self-reported impairment due to AUD in the past 12 months was assessed with the Sheehan Disability Scale (SDS) [32]. The scale represents five disability categories (no (0); mild (1-3); moderate (4-6); severe (7-9); and very severe (10) disability) with regard to four areas of role functioning (home management; work; maintaining relationships; and social life). At least moderate impairment was present if a 4 or higher was reported in at least one area of role functioning.

Number of weekly drinks in the past 12-months was computed by multiplying answers to two questions: "In the past 12 months, how often did you usually have at least one drink – every day, nearly every day, 3-4 days a week, 1-2 days a week, 1-3 days a month, or less than once a month?" and "On the days you drank in the past 12 months, about how many drinks did you usually have per day?". Four categories were then distinguished: abstinence or very low-risk drinking (≤ 7/14 drinks weekly for women/men); low-risk drinking (8-14/15-21 drinks weekly for women/men); medium-risk drinking (15-28/22-42 drinks weekly for women/men); and high-risk drinking (≥ 29/43 drinks weekly for women/men) [18]. Continuous variables regarding the number of weekly drinks at both waves were used to calculate the mean difference in number of weekly drinks between T_0 and T_1.

Psychiatric disorders and functioning. Psychiatric disorders were assessed with the CIDI 3.0. Included were 12-month emotional disorder consisting of mood disorder (major depression, dysthymia, bipolar disorder) and/or anxiety disorder (panic disorder, agoraphobia, social phobia, specific phobia, generalized anxiety disorder), and 12-month drug use disorder (drug abuse or dependence).

Functioning was assessed using two general functioning scales (ranging from 0 (poor) to 100 (good)), based on the eight SF-36 scales [33;34]: physical functioning (general health, physical health, physical functioning, and bodily pain; $\alpha = 0.78$) and mental functioning (psychological health, psychological functioning, social functioning, and vitality; $\alpha = 0.78$) [15]. Number of days lost from work or other activities in the past four weeks were measured with three questions from the WHO Disability Assessment Schedule; 'days out of role' [35].

Statistical analyses

The three groups (GenTx; AUDTx; NonTx) were compared on baseline and follow-up characteristics using multinomial regression analyses. To test for linear trends (p for trend), ordinal determinants were modeled as continuous variables. Analyses were performed using Stata version 12.1 [36]. The data were weighted to correct for differences in the response rates in different population groups at both waves and differences in the probability of respondent selection within households [26]. All analyses were adjusted for age, gender, and the time between T_0 and T_1. To account for multiple comparisons in this relatively small sample, a p-value < 0.01 was considered statistically significant.

RESULTS

Of the 154 subjects with baseline DSM-5 AUD, 19 (10.3%) received AUDTx during the study period, 50 (35.4%) received GenTx, and 85 (54.3%) did not receive any treatment (Table 6.1).

Group differences at baseline

Clinically, NonTx and GenTx users were very similar, but GenTx users were younger and more often without a partner (Table 6.1). The AUDTx group was quite different from the other two groups, including more often living without a partner, higher baseline severity on alcohol characteristics and more psychiatric disorders. More specifically, compared to NonTx use, AUDTx use was associated with higher rates of 12-month emotional disorder and 12-month drug use disorder, whereas compared to GenTx use, AUDTx use was associated with a higher rate of moderate impairment due to AUD and of 12-month emotional disorder.

Group differences at follow-up

AUD remission rates were similar for the GenTx and the NonTx users (63.9% vs. 77.9%, respectively) and much higher than the AUD remission rate for AUDTx users (28.9%) (Table 6.2).

Compared to NonTx users, GenTx users more often had a mild AUD at follow-up as well as a much higher rate of 12-month emotional disorder.

Compared to NonTx use, AUDTx use was associated with a higher number of DSM-5 AUD criteria at follow-up mainly due to the fact that moderate/severe AUD was much more frequent in AUDTx users than in NonTx users. In addition, AUDTx use was associated with significantly higher rates of 12-month emotional disorder and with worse mental and physical functioning.

Compared to GenTx use, AUDTx use was associated with a higher number of DSM-5 AUD criteria at follow-up mainly due to the fact that moderate/severe AUD was much more frequent in AUDTx users than in GenTx users. In addition, at least moderate impairment and high-risk drinking were more frequently present in AUDTx users than in GenTx users. No significant differences were observed between the two groups in psychiatric comorbidity, but mental functioning was worse in AUDTx.

How are non-treatment users getting on?

Of the three AUD groups, NonTx users had the most favorable follow-up status, but it is unclear whether their follow-up functioning is at a normal level. Therefore, a comparison with an extra reference group of non-treatment users without a lifetime AUD diagnosis and without lifetime psychiatric disorders at baseline (n = 2,747) was made. Logistic regression analyses adjusted for age, gender, and time between T_0 and T_1 revealed no significant group differences on any of the considered follow-up

Table 6.1. Baseline characteristics associated with general treatment utilization only (GenTx; n = 50) or alcohol use disorder (AUD) treatment utilization (AUDTx; n = 19) and with non-treatment (NonTx; n = 85) during the study period (4 years) among individuals with 12-month AUD at T_0.

					GenTx vs. NonTx [b]		AUDTx vs. NonTx [b]		AUDTx vs. GenTx [b]	
	All [a]	GenTx [a]	AUDTx [a]	NonTx [a]	OR_{adj}	(95% CI)	OR_{adj}	(95% CI)	OR_{adj}	(95% CI)
Total	100.0	35.4 (4.8)	10.3 (3.2)	54.3 (4.4)	-	-	-	-	-	-
Sociodemographics										
Male gender (%)	66.6 (5.0)	59.9 (10.7)	53.5 (18.1)	73.4 (6.8)	0.58	(0.15; 2.23)	0.36	(0.07; 1.85)	0.62	(0.11; 3.60)
Age (mean)	34.0 (1.3)	29.6 (1.2)	36.2 (5.9)	36.5 (1.8)	0.95*	(0.92; 0.98)	1.01	(0.95; 1.08)	1.06	(1.00; 1.13)
Low educational level (%)	33.2 (4.6)	21.8 (8.6)	61.0 (13.8)	35.3 (6.6)	0.41	(0.11; 1.43)	3.11	(0.79; 12.18)	7.67	(1.42; 41.52)
Living without a partner (%)	65.6 (3.9)	82.5 (4.6)	92.7 (4.8)	49.5 (6.6)	3.71*	(1.55; 8.89)	54.69**	(6.55; 456.64)	14.76*	(2.04; 106.80)
Unemployed (%)	20.8 (4.2)	22.1 (6.4)	60.0 (16.8)	12.4 (5.1)	1.71	(0.43; 6.77)	9.10	(1.37; 60.64)	5.34	(0.70; 40.79)
Not having enough income to live on (%)	14.3 (3.6)	24.4 (8.0)	12.6 (7.4)	8.0 (4.6)	2.40	(0.51; 11.34)	1.81	(0.19; 17.65)	0.76	(0.10; 5.90)
Characteristics of current AUD and drinking (%)										
Moderate/severe AUD: ≥ 4 criteria	30.9 (6.2)	25.2 (8.7)	82.1 (11.8)	24.9 (6.7)	0.84	(0.33; 2.13)	23.57	(1.72; 323.11)	28.10	(1.68; 469.31)
At least moderate 12-month impairment due to AUD	28.5 (5.4)	18.8 (6.5)	57.4 (15.0)	29.4 (7.4)	0.37	(0.13; 1.07)	4.79	(0.89; 25.93)	13.03*	(2.09; 81.21)
12-Month alcohol intake										
Abstinence or very low-risk drinking	34.4 (4.9)	41.9 (8.7)	23.5 (12.8)	31.7 (6.7)	1.00	-	1.00	-	1.00	-
Low-risk drinking	21.4 (4.6)	19.5 (8.3)	38.7 (18.7)	19.4 (5.0)	0.64	(0.18; 2.25)	2.43	(0.33; 17.78)	3.79	(0.37; 38.63)
Medium-risk drinking	30.0 (5.4)	27.2 (9.4)	9.7 (6.2)	35.8 (6.2)	0.53	(0.19; 1.46)	0.39	(0.04; 4.21)	0.73	(0.06; 9.19)
High-risk drinking	14.1 (3.8)	11.5 (5.3)	28.1 (12.2)	13.1 (6.1)	0.74	(0.14; 3.79)	5.07	(0.57; 45.16)	6.85	(1.05; 44.89)
P for trend					0.50		0.47		0.24	

Table 6.1 continues on the next page.

Table 6.1. *Continued.*

	All [a]	GenTx [a]	AUDTx [a]	NonTx [a]	GenTx vs. NonTx [b]		AUDTx vs. NonTx [b]		AUDTx vs. GenTx [b]	
					OR_{adj}	(95% CI)	OR_{adj}	(95% CI)	OR_{adj}	(95% CI)
Psychiatric comorbidity (%)										
12-Month emotional disorder	31.0 (4.6)	37.1 (7.9)	83.2 (8.7)	17.0 (5.7)	2.67	(0.79; 9.05)	21.34**	(4.39; 103.75)	8.00*	(1.91; 33.51)
12-Month drug disorder	10.5 (3.5)	13.1 (6.2)	37.4 (19.1)	3.6 (2.5)	3.00	(0.38; 23.49)	32.08*	(3.77; 273.02)	10.71	(1.01; 113.97)
Functioning (mean)										
Mental functioning (SF-36)	79.5 (1.9)	76.7 (3.1)	68.6 (2.9)	83.4 (2.3)	0.97	(0.94; 1.01)	0.95	(0.90; 0.99)	0.97	(0.94; 1.00)
Physical functioning (SF-36)	83.0 (1.6)	82.1 (2.2)	77.0 (6.1)	84.8 (2.4)	0.98	(0.95; 1.02)	0.97	(0.93; 1.00)	0.98	(0.95; 1.01)
Days out of role in last month	2.9 (0.6)	4.4 (1.5)	5.0 (1.9)	1.5 (0.5)	1.09	(1.01; 1.17)	1.08	(0.99; 1.17)	0.99	(0.94; 1.04)

Note. - Not calculated; * $p < 0.01$; ** $p < 0.001$.
[a] Percentages or means with the standard error between brackets.
[b] Odds ratios, adjusted for age, gender and time between T_0 and T_1, with 95% Confidence Intervals.

Table 6.2. Follow-up characteristics associated with general treatment utilization only (GenTx; n = 50) or alcohol use disorder (AUD) treatment utilization (AUDTx; n = 19) and with non-treatment (NonTx; n = 85) during the study period (4 years) among individuals with 12-month AUD at T_0.

	All [a]	GenTx [a]	AUDTx [a]	NonTx [a]	GenTx vs. NonTx [b]		AUDTx vs. NonTx [b]		AUDTx vs. GenTx [b]	
					OR_{adj}	(95% CI)	OR_{adj}	(95% CI)	OR_{adj}	(95% CI)
Characteristics of current AUD and drinking										
Number of 12-month AUD criteria (%)										
No disorder: 0-1 criterion	67.9 (4.2)	63.9 (8.1)	28.9 (12.2)	77.9 (6.6)	1.00	-	1.00	-	1.00	-
Mild: 2-3 criteria	17.7 (3.5)	32.8 (8.2)	13.0 (11.8)	8.8 (3.1)	4.16*	(1.56; 11.12)	2.17	(0.05; 91.45)	0.52	(0.02; 12.48)

Table 6.2 continues on the next page.

Table 6.2. *Continued.*

	All [a]	GenTx [a]	AUDTx [a]	NonTx [a]	GenTx vs. NonTx [b]		AUDTx vs. NonTx [b]		AUDTx vs. GenTx [b]	
					OR_{adj}	(95% CI)	OR_{adj}	(95% CI)	OR_{adj}	(95% CI)
Moderate/severe: ≥ 4 criteria	14.3 (4.1)	3.3 (3.3)	58.1 (15.3)	13.3 (6.2)	0.09	(0.01; 0.88)	21.65**	(6.25; 74.99)	230.24**	(22.62; 2343.14)
P for trend					0.39		< 0.001**		< 0.001**	
At least moderate 12-month impairment due to AUD (%)	15.0 (4.0)	3.6 (2.3)	56.1 (15.0)	14.7 (6.3)	0.10	(0.01; 0.94)	13.80	(1.34; 141.65)	135.63*	(4.16; 4422.28)
12-Month alcohol intake (%)										
Abstinence or very low-risk drinking	51.1 (4.9)	60.6 (9.1)	35.3 (13.3)	47.9 (7.0)	1.00	-	1.00	-	1.00	-
Low-risk drinking	22.2 (4.0)	24.7 (8.8)	6.6 (5.1)	23.6 (4.4)	0.61	(0.24; 1.56)	0.32	(0.03; 3.22)	0.52	(0.05; 5.86)
Medium-risk drinking	15.3 (3.3)	10.6 (4.8)	9.3 (6.1)	19.4 (6.0)	0.33	(0.07; 1.64)	0.36	(0.04; 3.03)	1.09	(0.17; 7.10)
High-risk drinking	11.4 (4.2)	4.1 (2.5)	48.8 (16.6)	9.1 (5.4)	0.31	(0.05; 1.82)	5.17	(0.84; 31.63)	16.53**	(3.35; 81.45)
P for trend					0.12		0.13		0.01*	
Mean change in number of drinks	-1.1 (3.4)	-7.1 (1.9)	3.8 (8.3)	1.9 (5.7)	0.97	(0.94; 1.00)	1.00	(0.98; 1.02)	1.03	(1.00; 1.07)
Psychiatric comorbidity (%)										
12-Month emotional disorder	21.5 (4.4)	40.2 (8.7)	44.8 (17.5)	4.9 (2.6)	13.82**	(4.86; 39.30)	13.13*	(2.61; 66.03)	0.95	(0.18; 4.92)
12-Month drug disorder	4.2 (2.9)	1.9 (1.9)	6.3 (4.9)	5.2 (5.0)	0.24	(0.01; 5.66)	1.86	(0.14; 24.17)	7.83	(0.58; 104.90)
Functioning (mean)										
Mental functioning (SF-36)	80.7 (1.0)	77.6 (1.9)	64.8 (5.0)	85.7 (1.3)	0.94	(0.88; 0.99)	0.90**	(0.85; 0.95)	0.96*	(0.93; 0.99)
Physical functioning (SF-36)	83.1 (1.2)	82.9 (1.9)	73.5 (5.8)	85.1 (1.8)	0.98	(0.95; 1.01)	0.95*	(0.91; 0.98)	0.96	(0.94; 0.99)
Days out of role in last month	3.5 (0.5)	4.9 (1.0)	6.1 (1.7)	2.0 (0.6)	1.09	(1.01; 1.18)	1.11	(1.01; 1.22)	1.02	(0.96; 1.08)

Note. - Not calculated; * $p < 0.01$; ** $p < 0.001$.

[a] Percentages or means with the standard error between brackets.

[b] Odds ratios, adjusted for age, gender and time between T_0 and T_1, with 95% Confidence Intervals.

characteristics (12-month emotional disorder, 12-month drug use disorder, mental and physical functioning, days out of role in the last month). Thus, NonTx users with baseline 12-month AUD had similar follow-up functioning as subjects from the general population without AUD and without other lifetime psychopathology; suggesting quite normal follow-up functioning.

DISCUSSION

This longitudinal general population study adds considerably to our insight in the magnitude and severity of the so-called treatment gap in subjects with an alcohol use disorder due to (1) the assessment of a broad range of severity characteristics, including alcohol intake; (2) the comparison of NonTx users with both GenTx users and AUDTx users; (3) the investigation of a relatively long period of treatment utilization (4 years) instead of the usual one year time frame; and (4) the comparison of NonTx AUD subjects with a non-AUD control group with respect to their follow-up functioning.

The study shows that the majority (54%) of the people with AUD in the general population receives no treatment at all during a 4-year period and that only a very small proportion receives AUDTx (10%). The study confirms earlier results that AUD severity is associated with AUDTx utilization, though unexpectedly, the level of alcohol intake played a limited role. GenTx users did not portray severe AUD characteristics. This is the first study to provide detailed information on how NonTx users are getting on. In general, they have a favorable AUD course with a very high AUD remission rate (78%) and the lowest severity on other clinical characteristics as compared to the other two treatment groups. Moreover, on average, at follow-up NonTx users were functioning at a level similar to subjects from the general population without a lifetime diagnosis of AUD and of other psychiatric disorders.

Limitations

First, the number of subjects with DSM-5 AUD at baseline was limited, resulting in limited power of the current analyses, thus precluding the detection of smaller effects or the use of multivariable regression models. Moreover, some large odds ratios and confidence intervals were observed, probably due to the small number of subjects in the AUDTx group. Replication of these findings in multivariable context and with other population-based samples is therefore needed. Second, as in other population-based studies [4;5], our treatment rates should be interpreted with some caution, because treatment refers to at least one contact made with a professional for AUD or for mental health or alcohol/drug problems. No detailed information on treatment setting or intensity was available and therefore no conclusions regarding treatment efficacy can be drawn. Third, in prospective studies, the internal validity of findings may be affected by selective attrition [37-39]. However, in NEMESIS-2, attrition was not associated with DSM-IV mental disorders after adjusting for sociodemographic characteristics [26] and

in the present study, treatment status at baseline was not associated with attrition. Therefore, sample attrition is unlikely to have affected our findings. Last, alcohol consumption and AUD diagnosis were exclusively based on self-report, thus recall bias might be an issue. For example regarding alcohol consumption, people may have difficulties remembering the amounts and frequencies in an average week. Moreover, reports on such behavior may be influenced by social stigma. These issues may have resulted in a general underestimation of alcohol consumption in all treatment groups [40]. However, it is not clear whether there were group differences in the level of underestimation which may have subsequently biased the group comparisons.

Findings

Generally low treatment rates were observed: less than half of the people with baseline AUD received any treatment during the study period, and only one-tenth used AUDTx. Notably, GenTx utilization, and to a greater extent AUDTx utilization, were strongly associated with living without a partner, consistent with previous research [9;10]. Possibly, relatively limited social resources result in a higher treatment need and a greater probability to seek treatment. Baseline clinical characteristics of GenTx and NonTx users were quite similar, except for the (non-significantly) higher rate of comorbid psychiatric disorders in the GenTx group. Specific AUDTx was mainly associated with more AUD-related impairments and a higher co-occurrence with emotional and drug use disorders compared to the other two groups. Extending observations from previous studies [2;11], these findings support that treatment seeking, also during a longer period, is mainly associated with the severity of the AUD, AUD related impairments and the presence of comorbid psychiatric disorders. This may point to a rather adequate process in which AUDTx utilization occurs when AUD reaches a critical level and natural remission is hard to achieve [11].

Findings regarding the longitudinal outcomes further confirm that a rather adequate treatment selection process seems to have taken place and that the observed low treatment utilization rate is not necessarily an indication of a large unmet need for treatment or a large treatment gap. Of those not receiving any treatment, 78% remitted from AUD and the large majority (91%) did not drink at high-risk at follow-up. These rates were quite similar for the GenTx users, but they reported a higher rate of mild AUD and more psychiatric comorbidity at follow-up than the NonTx users. Thus, even though these two groups were rather similar at baseline, mild but persistent problems or additional psychiatric disorders may have led GenTx users to seek treatment nonetheless. Finally, people who received AUDTx had the worst status at follow-up with regard to alcohol use and AUD characteristics as well as with regard to mental functioning. These findings indicate that it is probably not cost-effective to offer treatment to all those with AUD. The large majority of both NonTx and GenTx users adequately deal with the AUD and show considerable amelioration of AUD problems. At follow-up, NonTx users even function at a similar level as people who never had an AUD or

another psychiatric disorder. Moreover, those receiving AUDTx had the most severe and persistent problems. They are likely to perceive the highest need for care, though unfortunately, often with less than optimal outcomes [41].

Despite the finding that NonTx users generally have a favorable AUD course - with similar levels of functioning at follow-up compared to people who never had an AUD - it should be noted that an important minority of the NonTx users (22%) had a persistent AUD, and 60% of them had moderate or severe AUD at follow-up. It should be examined whether this severe subgroup would benefit from extra guidance to treatment. It may be that motivation for treatment is especially low in this group and possibly a brief and/or motivational intervention would be helpful to increase treatment entrance, as well as treatment compliance [42]. Barriers to seek treatment for alcohol problems may also include stigma associated with addiction treatment and fear of labelling [43]. E-health interventions should then be considered as these are often anonymous and therefore possibly less stigmatizing than regular treatment. Moreover, a significant subgroup of those with an AUD do not use AUDTx but only GenTx. This means that attention for alcohol problems in general treatment settings seems to be important. Specifically, although the diagnostic remission rate of 64% suggests that most of the GenTx users have a favorable AUD course, their alcohol problems should be noted so that timely interventions can be offered when the alcohol problems do not ameliorate.

Predictors of a persistent AUD course among GenTx and NonTx users were not examined in the current study, but previous population-based research showed that higher alcohol intake is associated with a poor AUD course, both in terms of persistency [18;24] and relapse [16;23;30]. As the present findings do not suggest that drinking is an important trigger for treatment utilization - no pronounced differences on baseline alcohol intake were observed between the three groups – this may point to possibilities to further improve treatment access. Possibly, positive attitudes towards drinking [44] hinder problem recognition and subsequently prevent that people feel a need for treatment, even though drinking levels and associated problems may reach a critical threshold. Primary care physicians may then be instrumental in the detection of NonTx users at risk of a severe AUD course [45]. That is, even though those individuals do not receive treatment for their mental problems, they may access primary care for physical disorders such as hypertension or diabetes, attention to alcohol intake is then desirable to increase awareness of the potential persistent problem.

Our follow-up findings also showed few significant differences in alcohol intake, with the exception of AUDTx users who were more often drinking at high-risk than GenTx users. This is in contrast to findings from the NESARC study, in which higher levels of recovery, including both diagnostic remission and abstinence or very low-risk drinking levels (< 7/14 drinks weekly for women/men) at follow-up, were observed in AUDTx users compared to NonTx users [12]. This incongruity in findings is difficult to explain, but may be due to methodological differences. NESARC only focused on 12-month treatment at baseline whereas in the present study, treatment could be present during

a 4-year period, including the 3 year prospective follow-up. Some of our AUDTx users may have just entered treatment at follow-up, thereby limiting the possibilities for a positive treatment outcome. Also, cross-national differences in treatment goals could play a role: abstinence is the dominant treatment goal in the US whereas in European countries, reduced risk drinking is more often considered a viable treatment option [46].

CONCLUSIONS

Our findings suggest that although the majority of subjects with AUD do not receive AUDTx, the problems associated with this so-called treatment gap seem limited as most NonTx and GenTx users show a favorable course of the disorder and of associated problems. The self-selection process that underlies treatment seeking and treatment utilization suggests a rational use of the limited treatment resources. However, some points for improvement could be noted. First, an important subgroup of NonTx users has a persistent course. It should be examined whether guidance to treatment would be beneficial for this group. Moreover, alcohol intake is an important marker for a severe AUD course [15;16;18;23;24] but plays a limited role in the decision to use treatment. Increased attention to level of intake in primary care may therefore be desirable to identify the subgroup of NonTx users at risk of a persistent AUD course. Lastly, monitoring of alcohol problems in GenTx settings is needed for the timely detection and treatment of persistent problems in this group.

REFERENCES

1. Grant B. F. Barriers to alcoholism treatment: Reasons for not seeking treatment in a general population sample. *J Stud Alcohol* 1997; **58**: 365-71.
2. Edlund M. J., Booth B. M., Han X. Who seeks care where? Utilization of mental health and substance use disorder treatment in two national samples of individuals with alcohol use disorders. *J Stud Alcohol Drugs* 2012; **73**: 635-46.
3. Bijl R. V., de Graaf R., Hiripi E., Kessler R. C., Kohn R., Offord D. R. *et al.* The prevalence of treated and untreated mental disorders in five countries. *Health Aff* 2003; **22**: 122-33.
4. ten Have M., de Graaf R., van Dorsselaer S., Beekman A. Lifetime treatment contact and delay in treatment seeking after first onset of a mental disorder. *Psychiatr Serv* 2013; **64**: 981-9.
5. Wang P.S., Angermeyer M., Borges G., Bruffaerts R., Tat C. W., de Girolamo G. *et al.* Delay and failure in treatment seeking after first onset of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* 2007; **6**: 177-85.
6. Bruffaerts R., Bonnewyn A., Demyttenaere K. Delays in seeking treatment for mental disorders in the Belgian general population. *Soc Psychiatry Psychiatr Epidemiol* 2007; **42**: 937-44.
7. Wang P. S., Berglund P., Olfson M., Pincus H. A., Wells K. B., Kessler R. C. Failure and delay in initial treatment contact after first onset of mental disorders in the National

Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 603-13.

8. Ilgen M. A., Price A. M., Burnett-Zeigler I., Perron B., Islam K., Bohnert A. S. B. *et al.* Longitudinal predictors of addictions treatment utilization in treatment-naïve adults with alcohol use disorders. *Drug Alcohol Depend* 2011; **113**: 215-21.
9. Oleski J., Mota N., Cox B. J., Sareen J. Perceived need for care, help seeking, and perceived barriers to care for alcohol use disorders in a national sample. *Psychiatr Serv* 2010; **61**: 1223-31.
10. Cohen E., Feinn R., Arias A., Kranzler H. R. Alcohol treatment utilization: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Depend* 2007; **86**: 214-21.
11. Grella C. E., Karno M. P., Warda U. S., Moore A. A., Niv N. Perceptions of need and help received for substance dependence in a national probability survey. *Psychiatr Serv* 2009; **60**: 1068-74.
12. Grella C. E., Stein J. A. Remission from substance dependence: differences between individuals in a general population longitudinal survey who do and do not seek help. *Drug Alcohol Depend* 2013; **133**: 146-53.
13. ten Have M., Nuijen J., Beekman A., de Graaf R. Common mental disorder severity and its association with treatment contact and treatment intensity for mental health problems. *Psychol Med* 2013; **43**: 2203-13.
14. Medina-Mora M. E., Borges G., Lara C., Benjet C., Blanco J., Fleiz C. *et al.* Prevalence, service use, and demographic correlates of 12-month DSM-IV psychiatric disorders in Mexico: results from the Mexican National Comorbidity Survey. *Psychol Med* 2005; **35**: 1773-83.
15. Tuithof M., ten Have M., van den Brink W., Vollebergh W., de Graaf R. The relationship between excessive alcohol consumption and alcohol use disorders according to DSM-IV and DSM-5. *Alcohol Clin Exp Res* 2014; **38**: 249-56.
16. Moos R. H., Moos B .S. Rates and predictors of relapse after natural and treated remission from alcohol use disorders. *Addiction* 2006; **101**: 212-22.
17. Lopez-Quintero C., Hasin D. S., de los Cobos J. P., Pines A., Wang S., Grant B. F. *et al.* Probability and predictors of remission from lifetime nicotine, alcohol, cannabis or cocaine dependence: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addiction* 2011; **106**: 657-69.
18. Tuithof M., ten Have M., Van den Brink W., Vollebergh W., de Graaf R. Predicting persistency of DSM-5 alcohol use disorder and examining drinking patterns of recently remitted individuals: a prospective general population study. *Addiction* 2013; **108**: 2091-9.
19. de Bruijn C., van den Brink W., de Graaf R., Vollebergh W. The three year course of alcohol use disorders in the general population: DSM-IV, ICD-10 and the Craving Withdrawal Model. *Addiction* 2006; **101**: 385-92.
20. Alonso J., Angermeyer M. C., Bernert S., Bruffaerts R., Brugha T. S., Bryson H. *et al.* Use of mental health services in Europe: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand* 2004; **109**: 47-54.
21. D'Amico E. J., Paddock S. M., Burnam A., Kung F. Y. Identification of and guidance for problem drinking by general medical providers: results from a national survey. *Med Care* 2005; **43**: 229-36.
22. O'Connor P. G., Nyquist J. G., McLellan A. T. Integrating addiction medicine into graduate medical education in primary care: the time has come. *Ann Intern Med* 2011; **154**: 56-9.
23. Dawson D. A., Goldstein R. B., Grant B. F. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: A 3-year follow-up. *Alcohol Clin Exp Res* 2007; **31**: 2036-45.

24. Dawson D. A., Goldstein R. B., Ruan W. J., Grant B. F. Correlates of recovery from alcohol dependence: A prospective study over a 3-year follow-up interval. *Alcohol Clin Exp Res* 2012; **36**: 1268-77.
25. de Graaf R., ten Have M., van Dorsselaer S. The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. *Int J Methods Psychiatr Res* 2010; **19**: 125-41.
26. de Graaf R., van Dorsselaer S., Tuithof M., ten Have M. Sociodemographic and psychiatric predictors of attrition in the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). *Compr Psychiatry* 2013; **54**: 1131-9.
27. Kessler R. C., Ustun T. B. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res* 2004; **13**: 93-121.
28. Haro J. M., Arbabzadeh-Bouchez S., Brugha T. S., De Girolamo G., Guyer M. E., Jin R. *et al.* Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. *Int J Methods Psychiatr Res* 2006; **15**: 167-80.
29. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Washington, DC: American Psychiatric Association (APA); 2013.
30. Tuithof M., ten Have M., Van den Brink W., Vollebergh W., de Graaf R. Alcohol consumption and symptoms as predictors for relapse of DSM-5 alcohol use disorder. *Drug Alcohol Depend* 2014; **140**: 85-91.
31. Mewton L., Slade T., Teesson M. An Evaluation of the Proposed DSM-5 Cannabis Use Disorder Criteria Using Australian National Survey Data. *J Stud Alcohol Drugs* 2013; **74**: 614-21.
32. Leon A. C., Olfson M., Portera L., Farber L., Sheehan D. V. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med* 1997; **27**: 93-105.
33. Stewart A. L., Hays R. D., Ware J. E. The MOS short-form general health survey: Reliability and validity in a patient population. *Med Care* 1988; **26**: 724-35.
34. Ware J. E., Sherbourne C. D. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473-83.
35. Von Korff M., Crane P. K., Alonso J., Vilagut G., Angermeyer M. C., Bruffaerts R. *et al.* Modified WHODAS-II provides valid measure of global disability but filter items increased skewness. *J Clin Epidemiol* 2008; **61**: 1132-43.
36. Statacorp. Stata Statistical Software: Release 12. College Station, Texas: Statacorp LP; 2011.
37. de Graaf R., Bijl R. V., Smit F., Ravelli A., Vollebergh W. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Am J Epidemiol* 2000; **152**: 1039-47.
38. Eaton W. W., Anthony J. C., Tepper S., Dryman A. Psychopathology and attrition in the epidemiologic catchment area surveys. *Am J Epidemiol* 1992; **135**: 1051-9.
39. Lamers F., Hoogendoorn A. W., Smit J. H., van Dyck R., Zitman F. G., Nolen W. A. *et al.* Sociodemographic and psychiatric determinants of attrition in the Netherlands Study of Depression and Anxiety (NESDA). *Compr Psychiatry* 2012; **53**: 63-70.
40. Stockwell T., Donath S., Cooper-Stanbury M., Chikritzhs T., Catalano P., Mateo C. Under-reporting of alcohol consumption in household surveys: a comparison of quantity-frequency, graduated-frequency and recent recall. *Addiction* 2004; **99**: 1024-33.
41. Merkx M. J., Schippers G. M., Koeter M. W., Vuijk P. J., Poch M., Kronemeijer H. *et al.* Predictive validity of treatment allocation guidelines on drinking outcome in alcohol-

dependent patients. *Addict Behav* 2013; **38**: 1691-8.

42. DiClemente C. C., Schlundt D., Gemmell L. Readiness and stages of change in addiction treatment. *Am J Addict* 2004; **13**: 103-19.
43. Fortney J., Mukherjee S., Curran G., Fortney S., Han X., Booth B. M. Factors associated with perceived stigma for alcohol use and treatment among at-risk drinkers. *J Behav Health Serv Res* 2004; **31**: 418-29.
44. Gordon R., Heim D., MacAskill S. Rethinking drinking cultures: a review of drinking cultures and a reconstructed dimensional approach. *Public Health* 2012; **126**: 3-11.
45. Angus C., Latimer N., Preston L., Li J., Purshouse R. What are the Implications for Policy Makers? A Systematic Review of the Cost-Effectiveness of Screening and Brief Interventions for Alcohol Misuse in Primary Care. *Front Psychiatry* 2014; **5**: 114.
46. van Amsterdam J., van den Brink W. Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. *J Psychopharmacol* 2013; **27**: 987-97.

Chapter 7

General discussion

KEY FINDINGS

This thesis confirms that most people in the general population with an alcohol use disorder have mild and transient problems, but also shows that an important minority suffers from severe and/or persistent problems. Importantly, most people with an alcohol use disorder in the general population do not drink excessively and this is even true for many of those with a large number of symptoms, i.e. those with DSM-IV alcohol dependence or with a moderate/severe DSM-5 alcohol use disorder. Nonetheless, excessive drinking is essential for the identification of people with a persistent alcohol use disorder, as are the number of alcohol use disorder criteria and the presence of comorbid psychiatric disorders (e.g. externalizing childhood disorders, adult anxiety disorder). Treatment seeking for alcohol use disorders is quite rare, but the mostly favorable course and the generally rational self-selection into treatment suggest that the public health relevance of this 'treatment gap' is limited.

METHODOLOGICAL CONSIDERATIONS

The findings in this thesis are based on data from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2). This longitudinal study investigates the presence and course of mental disorders in a representative sample of the Dutch general adult population [1]. Such data is quite unique: worldwide only a handful of similar studies were performed in the past three decades [2-8]. This kind of research provides important information for prevention programs, the optimization of guidelines, and the planning of treatment services. Yet, some important restrictions should be noted.

First, despite the overall representativeness of general population studies, some important subgroups are generally excluded, such as institutionalized or homeless individuals. Others are underrepresented, for example due to non-contact or refusal. Conceivably, heavy and problematic alcohol use are related to this selection, as it can be assumed that marginalized alcohol users are more often institutionalized or homeless, non-responders, or lost to follow-up. Thus, even though both response (65%) and retention rate (80%) of NEMESIS-2 are quite high, selection bias could be present and accordingly, a disproportionate number of people with (severe) alcohol use disorder may have been missed. Therefore, the prevalence, severity, persistence and the risk of relapse may have been underestimated in this thesis.

Second, most general population studies, including NEMESIS-2, rely on self-report. Generally, alcohol consumption observed in community studies is lower than the per capita alcohol consumption [9;10], suggesting underreporting. First, due to social stigma, people might be reluctant to report high alcohol consumption levels [11]. Also, the usual quantity of alcohol per drinking day tends to be lower than the arithmetic mean of a person's varying consumption pattern, since heavy drinking occasions are underrepresented in this measure [12] and no distinction is made between drinking

during weekdays and in the weekend in NEMESIS-2. Nonetheless, alcohol consumption in NEMESIS-2 was largely in agreement with the rates observed in other population-based studies in Western countries [13-15]. However, the prevalence of alcohol use disorder, and especially of alcohol dependence, was lower than what has previously been observed in general population studies, especially compared to the United States [16;17], but also in comparison to the first NEMESIS study [18]. As these previous high prevalence rates have been suggested to overestimate the problem, NEMESIS-2 findings may in fact represent a more realistic estimate [19]. Yet, methodological and cultural differences between the various studies cannot be precluded as sources of bias [20;21] and thus, NEMESIS-2 findings could underestimate the problem. Importantly, the low prevalence rate of alcohol dependence and thus of alcohol use disorders in NEMESIS-2 resulted in low statistical power for some of the analyses presented in this thesis.

Third, the choice for a dichotomous alcohol use disorder diagnosis imposes important restrictions. This dichotomy leads to an oversimplification of the gradual process associated with onset and course of alcohol use disorders: one symptom more or less can make the difference between fulfilling a diagnosis or not and hence, a negative outcome or not. This also implies that an unknown proportion of the observed transitions may be due to measurement error. Although DSM-5 still applies a single cut-off point for the presence or absence of the disorder, a severity indicator has been introduced: mild, moderate and severe alcohol use disorder based on the number of criteria. The present research was one of the first worldwide to examine the prevalence and course of DSM-5 alcohol use disorder in the general population while taking into account the role of this graded severity. Yet, it should be noted that the CIDI 3.0 used in the present research was designed and validated for the assessment of DSM-IV disorders [22], not for DSM-5 disorders. Although the criteria used in DSM-IV and DSM-5 are very similar, the reliability of the DSM-5 alcohol use disorder diagnosis based on the CIDI 3.0 is unknown and could be lower than for DSM-IV. More specific, the CIDI 3.0 assesses the DSM-IV clustering criterion (≥ 3 criteria in the same 12-month period for alcohol dependence), but not the DSM-5 clustering criterion (≥ 2 criteria in the same 12-month period). As this clustering criterion could not be part of the DSM-5 alcohol use disorder diagnosis, the prevalence, persistence and/or relapse of the disorder may have been overestimated.

Lastly, alcohol use disorders are complex maladaptive behaviors and there are many different ways to conceptualize the problem [23]. Recently, an overarching framework has been proposed (the COM-B model) suggesting that addictive behaviors (e.g. alcohol use disorder) are the result of three interacting conditions: *Capability* (e.g. deficient self-regulation), *Opportunity* (e.g. alcohol availability) and *Motivation* (e.g. relief from discomfort) [23]. This model describes a wide range of concepts that influence alcohol use disorders, including, but not limited to, the aspects examined in this thesis such as psychopathology (related to both motivation and capability) and socioeconomic status (related to opportunity). It should be noted that this integrated model (and other

models) contain many more predictors for the onset and course of alcohol use disorders than were examined in this thesis.

SUMMARY AND DISCUSSION OF FINDINGS

In **chapter 1**, the main objective of this thesis was explained: to enhance our understanding of the onset, course and treatment of alcohol use disorders in the general population. First, **chapter 2** examined the role of childhood attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) in the initiation of drinking and the onset of alcohol use disorders in order to improve our understanding of the groups in the general population that are more likely to develop alcohol problems. Second, the relationship between excessive drinking and alcohol use disorders was determined and characteristics associated with the presence of either one or both of these aspects of problematic alcohol use were examined (**chapter 3**). Third, it was investigated how many of those with an alcohol use disorder showed spontaneous remission (**chapter 4**) and relapse after initial remission (**chapter 5**). These chapters also examined predictors associated with a negative course. Fourth, **chapter 6** explored the magnitude and the nature of the 'treatment gap' by examining the percentage of people with an alcohol use disorder in contact with the treatment system and the main indicators for this process of treatment seeking. The main findings are summarized and discussed here.

Onset of drinking and of alcohol use disorders

Chapter 2 demonstrated that nearly all respondents ever consumed alcohol (94%), that the vast majority (86%) drank regularly at some point in their life (≥ 12 drinks per year), and that about one in five (19%) ever met criteria for a DSM-IV alcohol use disorder (abuse or dependence). The respective average ages of onset for these conditions were 15, 17 and 19 years. These high rates confirm that (regular) alcohol use is rather normative, but that most people seem to be able to control their drinking. Only a minority of all drinkers develop an alcohol use disorder, so targets for selective prevention are needed to efficiently prevent the development of alcohol use disorders. This thesis investigated two potential candidates: childhood ADHD and childhood CD.

Previous research has shown a strong link between substance use disorders and externalizing childhood disorders (ADHD and CD) [24-30]. The presence of such a relationship was confirmed in **chapter 2**, showing that childhood ADHD was associated with a higher prevalence of all stages of alcohol use and alcohol use related problems (i.e. alcohol initiation, regular alcohol use, and alcohol use disorder). Moreover, it was demonstrated that childhood ADHD is strongly related with CD and although CD was not associated with the first two stages of alcohol use (alcohol initiation and regular alcohol use), it was a strong predictor of alcohol use disorder and an earlier onset of the disorder. It should be noted that, after adjustment for age and sex, neither ADHD nor CD was associated with an earlier age of onset of (regular) alcohol use. Possibly

respondents' difficulties in remembering ages of onset challenged the detection of such an effect.

To interpret the relationship between ADHD, CD and alcohol use (disorder), two conceivable pathways were examined. The first pathway hypothesized that ADHD influences the development of CD, which in turn would result in a higher risk of alcohol use (disorder). Findings of **chapter 2** supported this pathway. When the relationship between childhood ADHD and the presence of an alcohol use disorder was adjusted for the presence of CD, this relationship was no longer statistically significant. In combination with the temporality in average ages of onset of ADHD (7 years), CD (12 years) and alcohol use disorder (19 years), these findings suggest the presence of an underlying developmental sequence. The second pathway hypothesized that children with both ADHD and CD represent a distinct subgroup with an especially high risk for alcohol use (disorder) compared to children with ADHD only or CD only. **Chapter 2** found no evidence for this proposition in an adult sample: a history with the combination of childhood ADHD and CD did not result in a particularly high risk of alcohol use (disorder) compared to a history with only ADHD or only CD.

The presence of an alcohol use disorder cannot be fully explained by the proposed developmental pathway: alcohol use disorders are more prevalent than CD and ADHD, and thus other pathways are operating as well [31]. Moreover, the effect of ADHD may not be fully explained by the simultaneous presence of CD [32]. Therefore, the current findings indicate that recognition of both ADHD and CD is important. Treatment of ADHD should preferably include measures to prevent the development CD and should ensure detection and treatment of CD when this occurs. Moreover, treatment of ADHD and of CD may help to prevent escalation of alcohol use and the development of alcohol use disorders [33-36]. Furthermore, the differential role of CD in the three stages of alcohol use (i.e. no role in the first two stages, but an important role in the last stage) illustrates that the influence of CD becomes stronger over time and this stresses the importance of the study of such processes while including all alcohol use disorders, not only those with an early onset as is done when using adolescent samples. The differential role of CD may also indicate that CD is associated only with the pathological aspects of alcohol use (and not with normative behaviors), possibly due to a phased expression of an underlying dimension of externalizing behavior [37;38]. It has been suggested that this underlying mechanism might be related to common neurobehavioral deficiencies in behavioral inhibition and reward sensitivity in ADHD and alcohol use disorders, possibly due to common genetic factors [39;40]. However, the role of CD in such a process is not well understood and the current findings suggest that this is an important avenue for future research.

Relationship between excessive drinking and alcohol use disorder

In **chapter 3**, the relationship between excessive alcohol consumption and the presence of an alcohol use disorder was examined. Even though it seems obvious that excessive

drinking is needed for an alcohol use disorder diagnosis, limited overlap was observed: of those with a DSM-IV alcohol use disorder only 18% reported excessive drinking (defined quite strictly as the presence of both high average consumption *and* frequent heavy drinking days). It should, however, be noted that the overlap was substantially higher for alcohol dependence (55%) than for alcohol abuse (10%). Overall, the DSM-5 diagnosis alcohol use disorder showed a larger overlap with excessive drinking (25%) than the DSM-IV diagnosis (18%). Yet, the overlap between mild DSM-5 alcohol use disorder and excessive drinking was still very small (17%), indicating that only moderate (30%) and particularly severe DSM-5 alcohol use disorder (65%) should be interpreted as equivalents of DSM-IV alcohol dependence.

Nonetheless, even though clinical research suggests that a persistent pattern of heavy drinking is needed to develop an alcohol use disorder [41], **chapter 3** confirmed that this might not be the case in the general population: non-heavy drinkers are identified as people having an alcohol use disorder diagnosis in the general population. This finding could have been a consequence of the strict definition of heavy drinking in the current study, but similar results were obtained with more lenient definitions of heavy drinking (i.e. high average alcohol consumption *or* frequent heavy drinking days). To better understand the reasons for this limited overlap, a series of *post-hoc* analyses were conducted looking at the historical relationship between excessive drinking and the presence of an alcohol use disorder diagnosis. These analyses showed that half of those with an alcohol use disorder but without excessive drinking did drink at a high level in the past. Conversely, more than one-third of those who drank excessively but did not have a 12-month alcohol use disorder had a lifetime history of an alcohol use disorder. The limited concurrent overlap could thus partly result from recovery from one aspect of problematic alcohol use (e.g. alcohol use disorder) whilst the other aspect continued to exist (e.g. excessive drinking).

In addition, we examined the differences between the subgroups of problematic alcohol users (excessive drinking only; alcohol use disorder only; both excessive drinking and alcohol use disorder) and non-problematic alcohol users. As compared to non-problematic drinkers, subjects of all three subgroups of problematic alcohol users on average also experienced more problems in domains of living other than drinking: more current mental disorders (mood, anxiety and drug use disorders), more childhood mental disorders (ADHD) and diminished mental functioning. All these subgroups thus seem clinically relevant and the magnitude of problematic alcohol use may therefore be bigger than assumed when only one aspect, either alcohol use disorder or excessive alcohol consumption, is considered. Nonetheless, the group with both aspects of problematic alcohol use was most affected and they had the highest rate of anxiety disorder, suicidal thoughts, and antisocial personality disorder. Notably, **chapter 3** also observed that low educational level, low income, and living without a partner occurred most frequently in this group. Together with similar observations in previous prospective research on

excessive drinking [42], this suggests that these sociodemographics may help to identify people at risk of severe problematic alcohol use.

The data of **chapter 3** are also relevant for the current discussion about the role of alcohol consumption in the definition of problematic alcohol use. DSM-5 has invoked discussions about the inclusion of a consumption criterion, including both mean daily alcohol consumption and the number of heavy drinking days [43;44]. Although this notion has been rejected, partly because of the lack of a cross-nationally accepted threshold for heavy alcohol use [45], it was recently proposed to identify problematic alcohol use solely based on the level of alcohol use [46]. A diagnosis based on a (complex) set of criteria was considered redundant mainly because heavy drinking would be a prerequisite for a diagnosis [46;47]. Although our data confirm that excessive drinking is important in the determination of severe problematic alcohol use, our data also show that the alcohol use disorder diagnosis is not redundant: there are people with an alcohol disorder without excessive drinking and these people would then be missed. It has been argued that these individuals are not much of public health concern as their drinking is within acceptable boundaries [46]. Yet, as described above, many of them have been drinking excessively in the past and current alcohol-related problems could indicate a continued struggle with maintaining a healthy drinking pattern. Also, the lack of excessive drinking in this group could reflect the individuals' difficulty in estimating their alcohol consumption levels [12], whereas the problems related to alcohol use might be easier to recognize and report. Research on these individuals with an alcohol use disorder but without excessive drinking is needed to better understand the nature of their problems. Furthermore, it is important to note that although excessive drinking in itself was associated with various other problems, these problems were worse for those who additionally had an alcohol use disorder. A study among the elderly showed a similar pattern [48] suggesting that the presence of alcohol-related problems is an indication of the urgency of the problematic alcohol use. Moreover, people who only consume excessively may need different motivational techniques to decrease their drinking pattern than people who perceive problems with alcohol use [49]. Altogether, the results of this thesis indicate that both aspects should be considered in clinical work (screening and monitoring) and in research, in order to establish optimal treatment.

Course of alcohol use disorders

To unravel why some individuals go into stable remission from alcohol problems while others do not, the course of alcohol use disorders in the adult general population was examined. Both 3-year persistence of alcohol use disorder (**chapter 4**) and relapse into another episode of alcohol use disorder among those in diagnostic remission (**chapter 5**) were studied. It was explicitly assessed whether individuals in diagnostic remission achieved abstinence or a (very) low level of drinking, and whether higher levels of drinking during remission were associated with an increased risk of relapse.

Persistence

In **chapter 4**, it was confirmed that DSM-5 alcohol use disorders in the general population generally show a favorable course: 70% showed diagnostic remission during a 3-year period. This is quite similar to findings of the first NEMESIS study regarding 3-year remission rates of DSM-IV alcohol dependence (74%), but lower than DSM-IV alcohol abuse (85%). It should be noted that the DSM-IV dependence diagnosis cannot be directly 'translated' to DSM-5 alcohol use disorders, thus similar remission rates do not equate to similar disorder severity. In fact, DSM-IV alcohol dependence likely implies greater severity, given its higher symptom threshold (3 out of 7 criteria) compared with DSM-5 alcohol use disorder (2 out of 11 criteria). For example, people meeting (several criteria of) DSM-IV alcohol abuse, possibly combined with one or two DSM-IV dependence criteria, would be in diagnostic remission of DSM-IV alcohol dependence, but persistent according to the DSM-5 diagnosis alcohol use disorder. Moreover, although the high remission rates of DSM-5 alcohol use disorder seem encouraging, they should be interpreted with some caution. While diagnostic remission of DSM-5 alcohol use disorder was associated with a decrease in drinking levels, abstinence was rarely achieved and more than one-third of the individuals in diagnostic remission still drank considerably (more than 7/14 drinks weekly for women/men). This puts them at risk of physical and mental harm related to excessive alcohol consumption [50-53] as well as relapse (**chapter 5**).

Nonetheless, within three years, spontaneous remission was frequently achieved and this suggests that it may not be necessary to offer expensive treatment to everyone with an alcohol use disorder in the general population: watchful waiting and/or brief interventions may be sufficient for most, whereas for some, more intensive treatment is needed. To identify those people at risk for a persistent course and more intensive treatment, a large number of predictors of persistence was studied in **chapter 4**, including many clinical and sociodemographic characteristics. Altogether, these predictors explained 25% of the variance in the persistence of alcohol use disorder. Other factors, not included in this study, thus also play a role in persistence of alcohol use disorders. This should be kept in mind when interpreting the results. Clinical characteristics related to the severity of problematic alcohol use predicted persistence: more alcohol use disorder criteria, disability due to alcohol use disorder and a larger number of weekly drinks. This is consistent with findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the only other longitudinal population-based study on predictors of persistence of alcohol use disorder (i.e. DSM-IV alcohol dependence) [54] and from a Dutch study on the 2-year persistence of alcohol dependence in a sample of mainly anxious or depressed individuals [55]. Robustness of findings is thus suggested. Importantly, **chapter 4** also showed that the number of weekly drinks predicted persistence independent of the number of alcohol use disorder criteria. This underscores that alcohol consumption may really help to identify patients with a persistent or even chronic alcohol use disorder.

Further determination of who is at risk of a persistent course of alcohol use disorder was difficult. Socioeconomic status (low educational level, unemployment, low income), smoking and vulnerability factors (e.g. childhood abuse) were not associated with a chronic course of an alcohol use disorder when other indicators were taken into account. However, *changes* in some of these factors (e.g. employment status, income and partner status) might be important in the prediction of persistence. For example, a recent study – also using data from NEMESIS-2 – observed that the economic crisis in the Netherlands was associated with an increase in the incidence of mental disorders [56]. It may very well be that such changes (at the population or the individual level) also play an important role in the persistence of an alcohol use disorder. Of the comorbid psychiatric disorders (mood, anxiety, drug use disorders) considered in **chapter 4**, only anxiety disorder emerged as an independent indicator of a persistent course. Clinical studies suggest that anxious people continue to use alcohol to alleviate their anxiety [57;58]; current findings provide first evidence that this might also be true in the general population. The role of the specific anxiety disorders in the course of alcohol use disorder in the general population is however still unknown and this should be addressed in future research.

Relapse

Chapter 5 showed that relapse after remission from an alcohol use disorder was rare in the general population. Only one in ten individuals in remission from a DSM-5 alcohol use disorder relapsed into a new episode within the course of three years. This corroborates previously observed DSM-IV relapse rates [51;55;59] and findings that alcohol use disorders are usually not chronic in the general population [60]. It was subsequently examined whether predictors of persistence (i.e. number of criteria of alcohol use disorder and level of alcohol consumption) were also predictors of relapse. **Chapter 5** indeed showed that more alcohol use disorder criteria (≥ 6 criteria) and a higher level of alcohol intake (more than 14/21 drinks weekly for women/men) were independently associated with a higher risk of relapse. Another new finding of **chapter 5** was that risky drinking (more than 7/14 drinks weekly for women/men) during remission strongly increased the risk of relapse, especially among people with a lifetime history of a severe alcohol use disorder and among people with higher past levels of alcohol consumption. Thus, even if people no longer experience problems with their alcohol use, continued risky drinking could indicate that they did not completely recover and accordingly, that they had an increased risk of relapse. On the other hand, abstinence at follow-up was rare but sustained remission was not. Therefore, psychologically of pharmacologically supported reduced drinking might be an option for recovery [61].

Chapter 5 also determined the predictive value of individual diagnostic criteria on relapse of alcohol use disorder. This is an under-researched issue even though previous community studies showed that specific symptoms differentially contribute to the incidence and persistence of substance use disorders [62-64]. Only lack of control

emerged as an important independent predictor of relapse. The importance of this symptom is not surprising as already in the early definitions of alcohol use disorder, lack of control was portrayed as a key element of maladaptive alcohol use [65;66]. Lack of control could be due to a deficiency in cognitive control (e.g. impulsivity) and/or the presence of increased drive/reward sensitivity [67]. Notably, both impulsivity and reward sensitivity also play a role in ADHD [39;67] and **chapter 2** showed that ADHD was significantly associated with alcohol use disorder via conduct disorder. The exact role of these neurobiological deficiencies in both onset and course of the disorders may thus be an important avenue for future research.

Treatment seeking for alcohol use disorders

Treatment seeking for an alcohol use disorder is quite rare in the general population. Only one in ten individuals with an alcohol use disorder established contact with a professional for alcohol-related problems within a 4-year period (**chapter 6**). Another third made contact with the health care system for other mental health problems. More than half of the people with an alcohol use disorder did not receive any professional treatment during a period of four years. These and similar findings (e.g. [68;69]) may be interpreted as an indication for the existence of a large treatment gap; an undesirable situation that needs to be resolved. However, given the mostly mild nature and benign course of alcohol use disorders in the general population (low persistence rate; **chapter 4** and low relapse rate; **chapter 5**), the clinical and societal relevance of such a 'treatment gap' can be questioned.

Findings in **chapter 6** indicate that treatment seeking for an alcohol use disorder is largely adequate, with those seeking such treatment meeting more alcohol use disorder criteria, having higher levels of impairment and having more comorbid mood or anxiety disorders than those not seeking alcohol treatment. This corresponds with previous research in the US [70;71] and this seems reassuring: the limited capacity of services is mostly used by individuals with the most severe clinical characteristics and the highest risk of persistence and not by less severe cases with a generally favorable natural course. A new finding was that those receiving treatment for other mental health problems more often had a comorbid emotional disorder than non-treatment users, suggestive of adequate treatment seeking. Importantly, low educational level or unemployment, were not associated with lower rates of treatment utilization. Strikingly, while this thesis consistently showed that the level of alcohol consumption plays a key role in predicting severity and course of alcohol use disorders, it only played a limited role in the decision to seek treatment.

Previous population-based research failed to examine the course of alcohol use disorders in people who decided not to seek treatment. However, such information is crucial to establish the clinical relevance of the treatment gap. Specifically, **chapter 6** showed high spontaneous remission rates for both non-treatment users (78%) and people using treatment for other mental health problems (64%). This is much higher

than the remission rate in the group using treatment services for their alcohol problems (29%), suggesting that many persistent cases adequately seek treatment from addiction treatment services. Moreover, especially in the group receiving treatment for other mental health problems, very few persistent cases had a moderate or severe alcohol use disorder at follow-up (10% as compared to 60% of the persistent cases without any treatment and 80% of the persistent cases with specialized alcohol treatment), indicating that the need for (additional) alcohol treatment is indeed very small in this group. **Chapter 6** further observed that long-term functioning of non-treatment users with an alcohol use disorder at baseline was similar to that of the healthy reference group (people from the general population who never had an alcohol use disorder or another mental disorder). This suggests that non-treatment users largely function at a normal level and their unmet need for treatment is likely limited to the individuals with a persistent disorder. It is uncertain whether this latter subgroup did actually perceive a need for treatment but did not access it due to perceived barriers or lack of motivation, or that there was no perceived need for treatment. This was not the subject of this thesis but such knowledge is important to develop better guidance to treatment for these individuals.

CLINICAL IMPLICATIONS

The findings in this thesis are not only of scientific interest, they are also of practical importance. Particularly, this thesis illustrates how common drinking alcohol is: the vast majority of the Dutch adults drinks and most people seem able to control their drinking. However, a minority of one in five adults develops an alcohol use disorder. It therefore seems efficient to tailor selective prevention to those individuals at risk of developing such a disorder. Most individuals with an alcohol use disorder experience mild and transient problems, but some suffer from severe and persistent problems. This indicates the importance of tailoring treatment intensity. In short, the findings of this thesis underscore that selective prevention is desirable, as well as treatment tailored to those individuals at risk of severe alcohol problems. Some suggestions are made here.

Selective prevention and treatment in youngsters

This thesis confirms that alcohol consumption as well as alcohol use disorder generally start at an early age. In combination with the observation that 'only' one in five alcohol users subsequently develop an alcohol use disorder, prevention methods tailored to youngsters at high risk for escalated alcohol use are highly recommended. Specifically, the observed developmental sequence from ADHD to alcohol use disorder via CD suggests that effective treatment of youngsters with these externalizing childhood disorders [33;34;72] may help to prevent the development of an alcohol use disorder. This treatment of ADHD and CD should also pay attention to the initiation of drinking

and development of alcohol-related problems [35;36;73]. Regarding CD, effective treatment can indeed prevent development of early onset substance use [35]. The effects of early ADHD treatment are, however, less clear. Although a recent meta-analysis suggested that stimulant treatment of children with ADHD has no influence on the risk of developing an adolescent or adult alcohol use disorder [73], a recent Dutch study showed that early stimulant treatment of children with ADHD prevented the development of a substance use disorder until at least age 17, even in those with severe ADHD or with comorbid CD [36]. In addition to medication, awareness of substance use in treatment of ADHD and CD may help to prevent subsequent alcohol use disorders and this thesis underscores the need for such a focus.

These findings also suggest that universal prevention programs directed at all school children need to be complemented with selective intervention programs directed at the relatively small group of children with an increased risk, including amongst others [31] children with ADHD/CD. As universal prevention programs with a parental component can reduce (heavy) weekly drinking in youngsters [74], such programs could serve as a first step to address underage drinking and accordingly reduce associated individual and societal costs. However, there is no proof that these universal prevention programs also prevent the development of alcohol use disorder and selective prevention therefore seems essential [75]. In fact, a selective alcohol intervention program that identifies adolescent risk groups (aged 13-15) who subsequently receive two 90 minute group sessions adapted to their personality profile (including profiles on sensation seeking and impulsivity) is currently being tested [76]. If this intervention proves to be effective, it may help to detect children with externalizing problems and address their drinking habits. Further, it could be used to identify those with serious externalizing problems and refer them for medication or behavioral therapy.

Prevention and treatment priorities among adults

This thesis consistently highlights the importance of both alcohol-related problems and excessive drinking to detect severe and/or chronic alcohol use disorder indicating that both aspects could serve as easily quantifiable risk markers for escalating problems. This is important, because the development of an alcohol use disorder is a gradual process with several intermediate stages. Findings of this thesis thereby extend previous suggestions to use staging and profiling for treatment allocation. Not only alcohol-related problems [77-79], but also excessive drinking, should be targeted by different treatment strategies ranging in intensity. It was beyond the scope of this thesis to specifically address best practices for different stages. Yet, moderate drinking levels and/or mild alcohol-related problems can effectively be targeted with low-intensity interventions in primary care such as effective e-health interventions [80] or brief motivational interventions [81], whereas for severe excessive drinking and/or moderate or severe alcohol use disorders additional pharmacotherapy or referral to specialized care may be indicated. Further research is needed to verify which cut-off points of

each dimension, alcohol-related problems and excessive drinking, offer the best match between patients and interventions (see Future studies).

Although **chapter 6** showed that the treatment seeking and selection process was generally adequate, some individuals with persistent alcohol problems did not establish contact with any professional about their alcohol problems or other mental health problems in a four-year period. These chronically ill individuals can be identified by the general practitioner (GP) or the primary care mental health nurse practitioner (so called MHNP or POH-GGZ) when the person is making a primary care visit for alcohol-related physical problems, e.g. hypertension [44]. Screening in the form of a short check-up of their alcohol use (e.g. AUDIT-C or Five shot) is an efficient way to signal alcohol problems [82]. Yet, these are currently not supported in guidelines for GPs, which only recommend assessment of drinking levels with no particular validated questions [83]. This thesis strongly advocates that screening directed at the level of alcohol consumption is complemented with a few questions about alcohol-related problems. GPs are often aware of the benefits of screening, but it is not always applied in a consistent manner [84]. Additional training of GPs during medical school on benefits of screening of alcohol problems has proven to increase the use of screening in the long-term [84], implementation of such extra training may be worthwhile for experienced GPs as well.

Importantly, this thesis points to various actions by the primary care MHNP once alcohol problems have been signaled. First, mostly mild alcohol use disorders were observed in the general population and these can be treated with low-intensity interventions. The MHNP could deliver brief motivational interventions addressing the level of alcohol use and mapping the pros and cons of drinking in a non-judgmental manner [85]. Second, the MHNP could promote e-health interventions addressing alcohol problems when individuals fear labeling or stigma. Alcoholism is a severely stigmatized mental disorder [86] and this could be a reason to reject face-to-face treatment. Many e-health interventions are both effective [80;87] and cost-effective [88], and are therefore valuable alternatives in such circumstances. Third, the findings of this thesis strongly suggest that interventions should be directed at abstinence or very low drinking levels, especially for those individuals with more severe clinical characteristics. Such a level may be achieved by brief interventions or cognitive behavior therapy, but some individuals prefer or need pharmacotherapy to reach this goal [89-92]. It would thus appear beneficial when the GP (assisted by the MHNP) can timely initiate pharmacological treatment. Fourth, as said, this thesis observed that persistent and relapsing alcohol problems are especially likely in individuals with many criteria of an alcohol use disorder and/or a high level of alcohol intake. Such individuals may be in need of intensive treatment that cannot be provided in primary care. The GP and the MHNP should be able to timely identify such individuals and refer them to specialized treatment [85]. Notably, these recommended actions are largely in accordance with recent transitions in the Dutch mental health care system, in which primary care is appointed a key role in the detection and treatment of mild mental health problems.

Monitoring of this transition seems advisable to ensure that it results in optimal care for people suffering from problematic alcohol use.

FUTURE RESEARCH

Findings of this thesis are among the first to examine prevalence and course of DSM-5 alcohol use disorder. This thesis showed that the presence of more DSM-5 criteria of alcohol use disorder was associated with a chronic course of the disorder. Still, DSM-5 has only recently been released and there remains much to be learned about the newly defined alcohol use disorder. First, more research is needed for a better understanding of the course of the disorder for each of the distinguished severity levels of the DSM-5 (mild, moderate, severe) as well as the transition from one severity level to the next. Inclusion of detailed data on when specific criteria are present or not may help future studies to understand such fluctuations in the course of the disorder. Second, this thesis showed that, while examining a broad range of static baseline characteristics, prediction of persistence and relapse is very challenging with only a small proportion of variance explained by the combination of baseline predictors. A similarly small predictive value was observed for the persistence of DSM-IV alcohol dependence [54]. As a consequence, it is difficult to develop and implement tailored treatments. However, qualitative research suggests that dynamic predictors (e.g. life events or changes in social relationships) are associated with a persistent course of cannabis dependence [93]. Examination of the direct relation between such dynamic, time-dependent factors and changes in severity of alcohol use disorder over time may thus be worthwhile. Third, DSM-5 alcohol use disorder is diagnosed when at least 2 of 11 criteria are present and the disorder can thus be heterogeneous. Our findings indicate that the presence of certain criteria can be important in the prediction of relapse. Similarly, a recent study suggested that a mixture of the number and type of criteria could be valuable to define the severity of the disorder [94]. Such combinations may also be used in the definition of adequate cut-off points for a stepped care approach.

This thesis showed that the level of excessive drinking plays a major role in the course of an alcohol use disorder. Thus, assessment of problematic alcohol use can be improved by inclusion of both alcohol use disorders and excessive drinking instead of only taking one aspect into account. Moreover, public health studies show that the level of drinking is exponentially associated with morbidity [95] and mortality [96]. Yet, the natural course of drinking patterns in the general population is largely unknown and needs to be studied more comprehensively. Although repeated measures of alcohol consumption in longitudinal population-based research are extremely valuable, inclusion of more advanced assessment techniques is needed to obtain detailed and ecological valid information. Specifically, momentary assessment could help to establish accurate information on drinking patterns and this can easily be applied via smart phones [12;97]. It may be efficient to apply such in-depth measures to a random subsample of a general

population study, with oversampling of individuals with alcohol use disorder symptoms. Alcohol consumption could then be monitored asking a few questions daily for a specific time period (e.g. one month) and could subsequently be linked to observed (alcohol-related) problems to further improve our understanding of this relationship.

Lastly, findings of this thesis suggest that developing and promoting a stepped care approach based on the underlying graded severity of problematic alcohol use should be guided by both the level of alcohol consumption and the number of alcohol use disorder criteria. Further research is however recommended to examine which interventions should be connected to each of these aspects of problematic alcohol use. Such studies should also focus on the identification of cut-off points as this is needed for a structured allocation of treatment. Of course, more factors play a role in the development and course of alcohol use disorders than excessive drinking and alcohol-related problems. This thesis also showed that symptom type, levels of impairment, and comorbid pathology (e.g. anxiety) play an important role in the course of the disorder. It should be noted that there are many other influences known to play a role in the development and course of alcohol use disorders, as is portrayed in a recent overarching framework presented by West [23]. This framework integrates the different theories that try to explain addictive behaviors, including theories covering automatic processes, neurobiological mechanisms, social network aspects and economic approaches. It is important to note that some of these other influences are also important for prevention, treatment seeking and treatment provision, e.g. social network aspects [98] and perceived stigma [99]. These aspects should thus also be taken into account when developing a stepped care approach for the treatment of alcohol use disorders (similar to the way this was done for depression [100]).

IN CONCLUSION

Alcohol use disorders among adults in the general population occur frequently (19%), but the disorder is often mild:

- 75-80% do not drink excessively
- 70% remits spontaneously within three years
- 12% of those in remission relapse in the course of three years

Only 10% of the people with an alcohol use disorder establish contact with a professional for these problems, but the treatment seeking seems to be quite adequate with those most in need of help having the highest contact rate. As only one in five adults develop an alcohol use disorder, it seems efficient to tailor selective prevention to those individuals at risk of developing such a disorder, and not to those who are able to control their drinking. As childhood externalizing disorders proved to be strong predictors of later alcohol problems, the need for early recognition and treatment of individuals with childhood ADHD or CD is highlighted. Moreover, the mild nature and

benign course of most alcohol use disorders suggests that it is efficient to allocate treatment resources to those at risk of a severe and/or chronic alcohol use disorder: those with a high drinking level, a high number of alcohol use disorder criteria, and comorbid psychopathology, specifically anxiety disorders. As the treatment gap (i.e. people with an alcohol use disorder not receiving treatment) appeared less problematic than often assumed, efforts to increase treatment access should primarily focus on the individuals at highest risk of a severe chronic course.

REFERENCES

1. de Graaf R., ten Have M., van Dorsselaer S. The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. *Int J Methods Psychiatr Res* 2010; **19**: 125-41.
2. de Graaf R., Bijl R.V., Smit F., Ravelli A., Vollebergh W. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Am J Epidemiol* 2000; **152**: 1039-47.
3. Grant B.F., Goldstein R.B., Chou S.P., Huang B., Stinson F.S., Dawson D.A. *et al.* Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *Mol Psychiatry* 2009; **14**: 1051-66.
4. Bijl R.V., de Graaf R., Ravelli A., Smit F., Vollebergh W. Gender and age-specific first incidence of DSM-III-R psychiatric disorders in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Soc Psychiatry Psychiatr Epidemiol* 2002; **37**: 372-9.
5. Lehtinen V., Sohlman B., Nummelin T., Salomaa M., Ayuso-Mateos J.L., Dowrick C. The estimated incidence of depressive disorder and its determinants in the Finnish ODIN sample. *Soc Psychiatry Psychiatr Epidemiol* 2005; **40**: 778-84.
6. Murphy J.M., Olivier D.C., Monson R.R., Sobol A.M., Leighton A.H. Incidence of depression and anxiety: the Stirling County Study. *Am J Public Health* 1988; **78**: 534-40.
7. Eaton W.W., Anthony J.C., Tepper S., Dryman A. Psychopathology and attrition in the epidemiologic catchment area surveys. *Am J Epidemiol* 1992; **135**: 1051-9.
8. Swendsen J., Conway K.P., Degenhardt L., Glantz M., Jin R., Merikangas K.R. *et al.* Mental disorders as risk factors for substance use, abuse and dependence: results from the 10-year follow-up of the National Comorbidity Survey. *Addiction* 2010; **105**: 1117-28.
9. Nelson D.E., Naimi T.S., Brewer R.D., Roeber J. US state alcohol sales compared to survey data, 1993-2006. *Addiction* 2010; **105**: 1589-96.
10. Stockwell T., Donath S., Cooper-Stanbury M., Chikritzhs T., Catalano P., Mateo C. Under-reporting of alcohol consumption in household surveys: a comparison of quantity-frequency, graduated-frequency and recent recall. *Addiction* 2004; **99**: 1024-33.
11. Welte J.W., Russell M. Influence of socially desirable responding in a study of stress and substance abuse. *Alcohol Clin Exp Res* 1993; **17**: 758-61.
12. Greenfield T.K., Kerr W.C. Alcohol measurement methodology in epidemiology: recent advances and opportunities. *Addiction* 2008; **103**: 1082-99.
13. Dawson D.A. Drinking patterns among individuals with and without DSM-IV alcohol use disorders. *J Stud Alcohol* 2000; **61**: 111-20.

14. Statistics Netherlands. *www.statline.cbs.nl*. Den Haag: Statistics Netherlands (CBS); 2015.
15. Dawson D.A., Goldstein R.B., Saha T.D., Grant B.F. Changes in alcohol consumption: United States, 2001-2002 to 2012-2013. *Drug Alcohol Depend* 2015; **148**: 56-61.
16. Grant B.F., Dawson D.A., Stinson F.S., Chou S.P., Dufour M.C., Pickering R.P. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug Alcohol Depend* 2004; **74**: 223-34.
17. Demyttenaere K., Bruffaerts R., Posada-Villa J., Gasquet I., Kovess V., Lepine J.P. *et al.* Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *JAMA* 2004; **291**: 2581-90.
18. Bijl R.V., Ravelli A., van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Soc Psychiatry Psychiatr Epidemiol* 1998; **33**: 587-95.
19. Wakefield J.C., Schmitz M.F. How many people have alcohol use disorders? Using the harmful dysfunction analysis to reconcile prevalence estimates in two community surveys. *Front Psychiatry* 2014; DOI: 10.3389/fpsyt.2014.00010.
20. Grucza R.A., Abbacchi A.M., Przybeck T.R., Gfroerer J.C. Discrepancies in estimates of prevalence and correlates of substance use and disorders between two national surveys. *Addiction* 2007; **102**: 623-9.
21. Verges A., Littlefield A.K., Sher K.J. Did lifetime rates of alcohol use disorders increase by 67% in 10 years? A comparison of NLAES and NESARC. *J Abnorm Psychol* 2011; **120**: 868-77.
22. Haro J.M., Arbabzadeh-Bouchez S., Brugha T.S., de Girolamo G., Guyer M.E., Jin R. *et al.* Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. *Int J Methods Psychiatr Res* 2006; **15**: 167-80.
23. West R. *EMCDDA Insights: Models of Addiction.* Luxembourg: Publication office of the European Union (EU); 2013.
24. Knop J., Penick E.C., Nickel E.J., Mortensen E.L., Sullivan M.A., Murtaza S. *et al.* Childhood ADHD and conduct disorder as independent predictors of male alcohol dependence at age 40. *J Stud Alcohol Drugs* 2009; **70**: 169-77.
25. Barkley R.A., Fischer M., Edelbrock C.S., Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry* 1990; **29**: 546-57.
26. Arias A.J., Gelernter J., Chan G., Weiss R.D., Brady K.T., Farrer L. *et al.* Correlates of co-occurring ADHD in drug-dependent subjects: Prevalence and features of substance dependence and psychiatric disorders. *Addict Behav* 2008; **33**: 1199-207.
27. Glantz M.D., Anthony J.C., Berglund P.A., Degenhardt L., Dierker L., Kalaydjian A. *et al.* Mental disorders as risk factors for later substance dependence: Estimates of optimal prevention and treatment benefits. *Psychol Med* 2009; **39**: 1365-77.
28. Elkins I.J., McGue M., Iacono W.G. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Arch Gen Psychiatry* 2007; **64**: 1145-52.
29. Milberger S., Biederman J., Faraone S.V., Wilens T., Chu M.P. Associations between ADHD and psychoactive substance use disorders: Findings from a longitudinal study of high-risk siblings of ADHD children. *Am J Addict* 1997; **6**: 318-29.
30. Biederman J., Wilens T.E., Mick E., Faraone S.V., Spencer T. Does attention-deficit hyperactivity disorder impact the developmental course of drug and alcohol abuse and dependence? *Biol Psychiatry* 1998; **44**: 269-73.

31. Zucker R.A. Anticipating problem alcohol use developmentally from childhood into middle adulthood: what have we learned? *Addiction* 2008; **103 Suppl 1**: 100-8.
32. Rodgers S., Muller M., Rossler W., Castelao E., Preisig M., Ajdacic-Gross V. Externalizing disorders and substance use: empirically derived subtypes in a population-based sample of adults. *Soc Psychiatry Psychiatr Epidemiol* 2015; **50**: 7-17.
33. Turgay A. Treatment of comorbidity in conduct disorder with attention-deficit hyperactivity disorder (ADHD). *Essent Psychopharmacol* 2005; **6**: 277-90.
34. van de Wiel N.M.H., Matthys W., Cohen-Kettenis P., van Engeland H. Application of the Utrecht Coping Power Program and care as usual to children with disruptive behavior disorders in outpatient clinics: A comparative study of cost and course of treatment. *Behavior Therapy* 2003; **34**: 421-36.
35. Zonnevylle-Bender M.J.S., Matthys W., van de Wiel N.M.H., Lochman J.E. Preventive effects of treatment of disruptive behavior disorder in middle childhood on substance use and delinquent behavior. *J Am Acad Child Adolesc Psychiatry* 2007; **46**: 33-9.
36. Groenman A.P., Oosterlaan J., Rommelse N.N., Franke B., Greven C.U., Hoekstra P.J. *et al.* Stimulant treatment for attention-deficit hyperactivity disorder and risk of developing substance use disorder. *Br J Psychiatry* 2013; **203**: 112-9.
37. White H.R., Xie M., Thompson W., Loeber R., Stouthamer-Loeber M. Psychopathology as a predictor of adolescent drug use trajectories. *Psychol Addict Behav* 2001; **15**: 210-8.
38. Kendler K.S., Prescott C.A., Myers J., Neale M.C. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry* 2003; **60**: 929-37.
39. Volkow N.D., Wang G.J., Kollins S.H., Wigal T.L., Newcorn J.H., Telang F. *et al.* Evaluating dopamine reward pathway in ADHD: clinical implications. *JAMA* 2009; **302**: 1084-91.
40. Derks E.M., Vink J.M., Willemsen G., van den Brink W., Boomsma D.I. Genetic and environmental influences on the relationship between adult ADHD symptoms and self-reported problem drinking in 6024 Dutch twins. *Psychol Med* 2014; **44**: 2673-83.
41. Storbjörk J., Room R. The two worlds of alcohol problems: Who is in treatment and who is not? *Addict Res Theory* 2008; **16**: 67-84.
42. van Oers J.A., Bongers I.M., van de Goor L.A., Garretsen H.F. Alcohol consumption, alcohol-related problems, problem drinking, and socioeconomic status. *Alcohol Alcohol* 1999; **34**: 78-88.
43. Saha T.D., Stinson F.S., Grant B.F. The role of alcohol consumption in future classifications of alcohol use disorders. *Drug Alcohol Depend* 2007; **89**: 82-92.
44. Li T.K., Hewitt B.G., Grant B.F. Is there a future for quantifying drinking in the diagnosis, treatment, and prevention of alcohol use disorders? *Alcohol Alcohol* 2007; **42**: 57-63.
45. Hasin D.S., O'Brien C.P., Auriacombe M., Borges G., Bucholz K., Budney A. *et al.* DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry* 2013; **170**: 834-51.
46. Rehm J., Marmet S., Anderson P., Gual A., Kraus L., Nutt D.J. *et al.* Defining substance use disorders: do we really need more than heavy use? *Alcohol Alcohol* 2013; **48**: 633-40.
47. Nutt D.J., Rehm J. Doing it by numbers: a simple approach to reducing the harms of alcohol. *J Psychopharmacol* 2014; **28**: 3-7.
48. Sacco P., Bucholz K.K., Spitznagel E.L. Alcohol use among older adults in the National Epidemiologic Survey on Alcohol and Related Conditions: A latent class analysis. *J Stud Alcohol Drugs* 2009; **70**: 829-38.
49. Heather N. A radical but flawed proposal: comments on Rehm et al. 'Defining substance use disorders: do we really need more than heavy use?'. *Alcohol Alcohol* 2013; **48**: 646-7.

50. Rehm J., Baliunas D., Borges G.L.G., Graham K., Irving H., Kehoe T. *et al.* The relation between different dimensions of alcohol consumption and burden of disease: An overview. *Addiction* 2010; **105**: 817-43.
51. Dawson D.A., Goldstein R.B., Grant B.F. Rates and correlates of relapse among individuals in remission from DSM-IV alcohol dependence: A 3-year follow-up. *Alcohol Clin Exp Res* 2007; **31**: 2036-45.
52. Moos R.H., Moos B.S. Rates and predictors of relapse after natural and treated remission from alcohol use disorders. *Addiction* 2006; **101**: 212-22.
53. World Health Organization. *International guide for monitoring alcohol consumption and related harm.* Geneva: World Health Organization (WHO); 2000.
54. Dawson D.A., Goldstein R.B., Ruan W.J., Grant B.F. Correlates of recovery from alcohol dependence: A prospective study over a 3-year follow-up interval. *Alcohol Clin Exp Res* 2012; **36**: 1268-77.
55. Boschloo L., Vogelzangs N., van den Brink W., Smit J.H., Beekman A.T.F., Penninx B.W.J.H. Predictors of the 2-year recurrence and persistence of alcohol dependence. *Addiction* 2012; **107**: 1639-40.
56. Barbaglia M.G., ten Have M., van Dorsselaer S., Alonso J., de Graaf R. Negative socioeconomic changes and mental disorders: a longitudinal study. *J Epidemiol Community Health* 2015; **69**: 55-62.
57. Kushner M.G., Abrams K., Borchardt C. The relationship between anxiety disorders and alcohol use disorders: A review of major perspectives and findings. *Clin Psychol Rev* 2000; **20**: 149-71.
58. Crum R.M., Mojtabai R., Lazareck S., Bolton J.M., Robinson J., Sareen J. *et al.* A prospective assessment of reports of drinking to self-medicate mood symptoms with the incidence and persistence of alcohol dependence. *JAMA Psychiatry* 2013; **70**: 718-26.
59. de Bruijn C., van den Brink W., de Graaf R., Vollebergh W.A.M. The three year course of alcohol use disorders in the general population: DSM-IV, ICD-10 and the Craving Withdrawal Model. *Addiction* 2006; **101**: 385-92.
60. Cunningham J.A., McCambridge J. Is alcohol dependence best viewed as a chronic relapsing disorder? *Addiction* 2012; **107**: 6-12.
61. van Amsterdam J., van den Brink W. Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. *J Psychopharmacol* 2013; **27**: 987-97.
62. de Graaf R., Bijl R.V., Ravelli A., Smit F., Vollebergh W.A. Predictors of first incidence of DSM-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health Survey and Incidence Study. *Acta Psychiatr Scand* 2002; **106**: 303-13.
63. de Bruijn C., van den Brink W., de Graaf R., Vollebergh W. Alcohol abuse and dependence criteria as predictors of a chronic course of alcohol use disorders in the general population. *Alcohol Alcohol* 2005; **40**: 441-6.
64. van der Pol P., Liebregts N., de Graaf R., Korf D.J., van den Brink W., van Laar M. Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study. *Drug Alcohol Depend* 2013; **133**: 352-9.
65. Jellinek E.M. *The Disease Concept of Alcoholism*. New Brunswick: Hillhouse Press; 1960.
66. Edwards G., Gross M.M. Alcohol dependence: provisional description of a clinical syndrome. *Br Med J* 1976; **1**: 1058-61.
67. Wilens T.E., Morrison N.R. The intersection of attention-deficit/hyperactivity disorder and substance abuse. *Curr Opin Psychiatry* 2011; **24**: 280-5.
68. Alonso J., Angermeyer M.C., Bernert S., Bruffaerts R., Brugha T.S., Bryson H. *et al.* Use of mental health services in Europe: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand* 2004; **109**: 47-54.

69. Kohn R., Saxena S., Levav I., Saraceno B. The treatment gap in mental health care. *Bull World Health Organ* 2004; **82**: 858-66.
70. Edlund M.J., Booth B.M., Han X. Who seeks care where? Utilization of mental health and substance use disorder treatment in two national samples of individuals with alcohol use disorders. *J Stud Alcohol Drugs* 2012; **73**: 635-46.
71. Kaufmann C.N., Chen L.Y., Crum R.M., Mojtabai R. Treatment seeking and barriers to treatment for alcohol use in persons with alcohol use disorders and comorbid mood or anxiety disorders. *Soc Psychiatry Psychiatr Epidemiol* 2014; **49**: 1489-99.
72. Chronis A.M., Jones H.A., Raggi V.L. Evidence-based psychosocial treatments for children and adolescents with attention-deficit/hyperactivity disorder. *Clin Psychol Rev* 2006; **26**: 486-502.
73. Humphreys K.L., Eng T., Lee S.S. Stimulant medication and substance use outcomes: a meta-analysis. *JAMA Psychiatry* 2013; **70**: 740-9.
74. Koning I.M., van den Eijnden R.J., Verdurmen J.E., Engels R.C., Vollebergh W.A. A cluster randomized trial on the effects of a parent and student intervention on alcohol use in adolescents four years after baseline; no evidence of catching-up behavior. *Addict Behav* 2013; **38**: 2032-9.
75. van Laar M., Cruts G., van Ooyen-Houben M., Croes E., van der Pol P., Meijer R. *et al. Nation Report 2014: Netherlands: report to the EMCDDA by the Reitox National Focal Point.* Utrecht/Den Haag: Trimbos/WODC; 2015.
76. Lammers J., Goossens F., Lokman S., Monshouwer K., Lemmers L., Conrod P. *et al.* Evaluating a selective prevention programme for binge drinking among young adolescents: study protocol of a randomized controlled trial. *BMC Public Health* 2011; **11**: 126.
77. van den Brink W., Schippers G.M. Stagering en profilering bij verslaving (Staging and profiling in addiction). *Tijdschr Psychiatr* 2012; **54**: 941-8.
78. Merkx M.J., Schippers G.M., Koeter M.W., Vuijk P.J., Poch M., Kronemeijer H. *et al.* Predictive validity of treatment allocation guidelines on drinking outcome in alcohol-dependent patients. *Addict Behav* 2013; **38**: 1691-8.
79. Merkx M.J., Schippers G.M., Koeter M.J., Vuijk P.J., Oudejans S., de Vries C.C. *et al.* Allocation of substance use disorder patients to appropriate levels of care: feasibility of matching guidelines in routine practice in Dutch treatment centres. *Addiction* 2007; **102**: 466-74.
80. Blankers M., Nabitz U., Smit F., Koeter M.W., Schippers G.M. Economic evaluation of internet-based interventions for harmful alcohol use alongside a pragmatic randomized controlled trial. *J Med Internet Res* 2012; **14**: e134.
81. Harris S.K., Louis-Jacques J., Knight J.R. Screening and brief intervention for alcohol and other abuse. *Adolesc Med State Art Rev* 2014; **25**: 126-56.
82. Rubinsky A.D., Dawson D.A., Williams E.C., Kivlahan D.R., Bradley K.A. AUDIT-C scores as a scaled marker of mean daily drinking, alcohol use disorder severity, and probability of alcohol dependence in a U.S. general population sample of drinkers. *Alcohol Clin Exp Res* 2013; **37**: 1380-90.
83. Nederlands Huisartsen Genootschap. *NHG-standaard problematisch alcoholgebruik*. Utrecht: Nederlands Huisartsen Genootschap (NHG); 2014.
84. Siegal H.A., Cole P.A., Li L., Eddy M.F. Can a brief clinical practicum influence physicians' communications with patients about alcohol and drug problems? Results of a long-term follow-up. *Teach Learn Med* 2000; **12**: 72-7.
85. Babor T.F., McRee B.G., Kassebaum P.A., Grimaldi P.L., Ahmed K., Bray J. Screening, Brief Intervention, and Referral to Treatment (SBIRT): toward a public health approach to the management of substance abuse. *Subst Abus* 2007; **28**: 7-30.
86. Schomerus G., Lucht M., Holzinger A., Matschinger H., Carta M.G., Angermeyer

M.C. The stigma of alcohol dependence compared with other mental disorders: a review of population studies. *Alcohol Alcohol* 2011; **46**: 105-12.

87. Riper H., Spek V., Boon B., Conijn B., Kramer J., Martin-Abello K. *et al.* Effectiveness of E-self-help interventions for curbing adult problem drinking: a meta-analysis. *J Med Internet Res* 2011; **13**: e42.
88. Suijkerbuijk A.V.M., van Gils P.F., van Gils G.A. *De kosteneffectiviteit van interventies gericht op verslaving aan alcohol en middelen: Een review van de literatuur.* Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM); 2014.
89. Rosner S., Hackl-Herrwerth A., Leucht S., Vecchi S., Srisurapanont M., Soyka M. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev* 2010; CD001867.
90. van den Brink W., Sorensen P., Torup L., Mann K., Gual A. Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. *J Psychopharmacol* 2014; **28**: 733-44.
91. van den Brink W., Aubin H.J., Bladstrom A., Torup L., Gual A., Mann K. Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: results from a subgroup analysis of two randomized controlled 6-month studies. *Alcohol Alcohol* 2013; **48**: 570-8.
92. Rosner S., Hackl-Herrwerth A., Leucht S., Lehert P., Vecchi S., Soyka M. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev* 2010; CD004332.
93. Liebregts N., van der Pol P., de Graaf R., van Laar M., van den Brink W., Korf D.J. Persistence and desistance in heavy cannabis use: the role of identity, agency, and life events. *Journal of youth studies* 2014; DOI: 10.1080/13676261.2014.992320.
94. Preuss U.W., Watzke S., Wurst F.M. Dimensionality and stages of severity of DSM-5 criteria in an international sample of alcohol-consuming individuals. *Psychol Med* 2014; **44**: 3303-14.
95. Rehm J., Mathers C., Popova S., Thavorncharoensap M., Teerawattananon Y., Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; **373**: 2223-33.
96. Rehm J., Shield K.D., Gmel G., Rehm M.X., Frick U. Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *Eur Neuropsychopharmacol* 2013; **23**: 89-97.
97. Shiffman S. Ecological momentary assessment (EMA) in studies of substance use. *Psychol Assess* 2009; **21**: 486-97.
98. Longabaugh R., Wirtz P.W., Zywiak W.H., O'Malley S.S. Network support as a prognostic indicator of drinking outcomes: the COMBINE Study. *J Stud Alcohol Drugs* 2010; **71**: 837-46.
99. Schomerus G., Corrigan P.W., Klauer T., Kuwert P., Freyberger H.J., Lucht M. Self-stigma in alcohol dependence: consequences for drinking-refusal self-efficacy. *Drug Alcohol Depend* 2011; **114**: 12-7.
100. Nederlands Huisartsen Genootschap. *NHG-standaard depressie.* Utrecht: Nederlands Huisartsen Genootschap (NHG); 2012.

Summary

BACKGROUND

Although drinking alcohol is common and regarded to be normal behavior in Western society, some people drink excessively and develop drinking problems. When these problems severely disrupt people's life, an alcohol use disorder is considered present and this disorder is associated with substantial disease burden and mortality. Therefore, prevention and treatment of alcohol use disorders should be a public health priority. In order to plan prevention and treatment, information is needed about alcohol use disorders, their course and their risk indicators in the general population. However, current knowledge on these disorders is largely restricted to findings from clinical samples, whereas most people with an alcohol use disorder do not enter treatment. The reasons for not seeking treatment are largely unknown, but it seems likely that people who do not seek treatment drink less or experience only mild problems. Therefore, findings from clinical samples cannot be extrapolated to the general population and important questions that need to be addressed in the general population include:

- Which people are at risk of developing an alcohol use disorder?
- To which degree are alcohol use disorders related to the level of alcohol consumption?
- What determines whether individuals with an alcohol use disorder reach (stable) remission while others do not?
- Is treatment seeking related to the level of drinking or the severity of the alcohol use disorder?

In this thesis, these questions were studied using data from the second Netherlands Mental Health Survey and Incidence Study (NEMESIS-2), including 6,646 Dutch adults (aged 18-64) at baseline and 5,303 at 3-year follow-up. NEMESIS-2 is an ongoing psychiatric epidemiological cohort study recording detailed information on prevalence, incidence, course and consequences of mental disorders, including alcohol use disorders, in a representative sample of the Dutch adult population.

Onset of drinking and of alcohol use disorders

Chapter 2 showed that almost all study participants ever consumed alcohol (94%), that the vast majority of the participants (86%) ever drank regularly (≥ 12 drinks per year), and that about one in five (19%) ever met criteria for an alcohol use disorder. Next, **chapter 2** examined two potential risk factors for the development of alcohol use and alcohol use disorders in the general population: childhood attention-deficit/ hyperactivity disorder (ADHD) and childhood conduct disorder. Adults who had ADHD when they were young more often started to drink alcohol and to drink regular and they had a bigger risk to develop an alcohol use disorder. Childhood conduct disorder did not predict the onset of (regular) alcohol use, but it was a strong predictor of the development of an alcohol use disorder. Further analyses showed that ADHD and

conduct disorder were strongly related and when the relationship between childhood ADHD and the presence of an alcohol use disorder was adjusted for the presence of conduct disorder, this relationship was no longer significant. In combination with the mean ages of onset of ADHD, conduct disorder, and alcohol use disorders (7, 12 and 19 years old, respectively), these findings support the hypothesis of an underlying developmental sequence: ADHD increases the risk of conduct disorder and conduct disorder in turn increases the risk of an alcohol use disorder. Early interventions among children with ADHD may prevent progress from ADHD into conduct disorder and subsequent alcohol use disorder. Attention to the initiation of drinking and development of alcohol-related problems in treatment of children with ADHD or conduct disorder might further prevent escalation of alcohol use.

Relationship between excessive drinking and alcohol use disorder

While one may expect that excessive drinking is needed for the development of an alcohol use disorder, only very limited overlap was observed in **chapter 3**: of those with an alcohol use disorder only 18% reported excessive drinking. Excessive drinking was defined quite strictly (requiring both high average consumption *and* frequent heavy drinking days), but the limited overlap was still observed when the definition of excessive drinking was eased. To understand this limited overlap between excessive alcohol consumption and alcohol use disorder, the differences between subgroups of problematic alcohol users (excessive drinking only; alcohol use disorder only; both excessive drinking and alcohol use disorder) and non-problematic alcohol users were mapped. As compared to non-problematic drinkers, subjects of the other three groups experienced more problems in domains of living other than drinking: higher rates of 12-month mental disorders (mood, anxiety and drug use disorders), higher rates of ADHD and diminished functioning. All three groups had clinically relevant problems. However, the group with both excessive drinking and alcohol use disorder had the highest rate of anxiety disorder, suicidal thoughts, and antisocial personality disorder. Furthermore, **chapter 3** showed that low educational level, low income, and living without a partner occurred most frequently in the individuals with both aspects of problematic alcohol use. Together with similar observations in previous prospective research on excessive drinking, this suggests that these sociodemographics may help to identify people at risk of severe problematic alcohol use. All in all, the results of **chapter 3** indicate that both excessive drinking *and* alcohol use disorder should be considered in research as well as in screening and monitoring in clinical practice.

Course of alcohol use disorders

Chapter 4 demonstrated that alcohol use disorders in the general population generally showed a favorable course: 70% achieved diagnostic remission during a 3-year period. This high remission rate should, however, be interpreted with caution: more than one-third of those in diagnostic remission still drank considerable (more than 7 drinks

per week for women or more than 14 drinks per week for men). Clinical characteristics were most important in the detection of individuals with a persistent alcohol use disorder (e.g. a larger number of alcohol use disorder criteria, alcohol-related disability and higher number of weekly drinks). Sociodemographics, comorbid mood and drug use disorder, smoking and vulnerability indicators (e.g. parental psychopathology and childhood maltreatment) were not associated with a persistent course. However, the presence of a co-morbid anxiety disorder did add to the prediction of persistence. Together, the observed predictors explained only 25% of the variance in the persistence of alcohol use disorder, so other factors must play a role as well.

Chapter 5 showed that in the general population relapse after remission from an alcohol use disorder was rare. In the course of three years, only 12% of the people in diagnostic remission from an alcohol use disorder relapsed into a new episode. Similar to persistence, the number of alcohol use disorder criteria (≥ 6 criteria) and a higher level of alcohol intake (ever more than 14/21 drinks per week for women/men) were independently associated with a higher risk of relapse. Furthermore, risky drinking during remission (more than 7/14 drinks per week for women/men) strongly increased the risk of relapse, particularly among people with a lifetime history of a severe alcohol use disorder and among people with higher past levels of alcohol consumption. This suggests that drinking habits during remission should be an important target for treatment and relapse prevention. Particularly, people who have a history of severe alcohol problems may benefit from abstinence or (very) low drinking levels. Controlled drinking at higher levels may only be possible for those without a history of severe alcohol problems or in combination with pharmacotherapy.

Treatment seeking for alcohol use disorders

Chapter 6 showed that during a 4-year period, only one in ten individuals with an alcohol use disorder made contact with a professional for alcohol-related problems. Another third made contact with the health care system for other mental health problems, whereas more than half of the people with an alcohol use disorder did not receive any professional treatment during a period of four years, indicating the presence of a serious 'treatment gap'. Those seeking alcohol treatment met more alcohol use disorder criteria, had higher levels of impairment and more comorbid mood or anxiety disorders than those not seeking alcohol treatment. This suggests that the choice whether or not to seek alcohol treatment is largely adequate. Those receiving treatment for other mental health problems had more comorbid emotional disorders than non-treatment users, which also points to adequate treatment seeking. Moreover, both non-treatment users and people using treatment for other mental health problems showed high spontaneous remission rates of their alcohol use disorder, 78% and 64% respectively. This is much higher than the remission rate in the group using addiction treatment services for their alcohol problems (29%), indicating that mainly those with a persistent alcohol use disorder contacted the alcohol treatment services. Lastly, the

follow-up functioning of non-treatment users with an alcohol use disorder at baseline was similar to that of a healthy reference group (subjects from the general population who never had an alcohol use disorder or another mental disorder). Non-treatment users thus seem to function largely at a normal level and their unmet need for treatment is likely limited to the small group with a persistent disorder (i.e. 22% of the non-treatment users). In summary, the 'treatment gap' seems less problematic than often assumed. Those who appear to have a high treatment need mostly find their way into treatment and those who do not seek treatment generally have mild problems with a favorable course. This suggests that the limited treatment resources are used quite rationally.

DISCUSSION

The vast majority of the Dutch adults ever started drinking alcohol and one in five develop an alcohol use disorder. Importantly, adults who have had an externalizing childhood disorder more often developed an alcohol use disorder: a pathway was observed from childhood ADHD to alcohol use disorder via childhood conduct disorder. Although other risk indicators will play a role as well, this pathway stresses the need for recognition and early treatment of externalizing childhood disorders to prevent development of alcohol use disorders.

Notably, most people with an alcohol use disorder in the general population have mild and transient problems: 75-80% do not drink excessively, 70% remits spontaneously within three years and only 12% of those in remission show a relapse. It thus seems efficient to allocate treatment resources to those at risk of a severe and/or chronic alcohol use disorder: those with a high drinking level, a high number of alcohol use disorder criteria, and comorbid psychopathology, specifically anxiety disorders.

Despite the fact that only 10% of the individuals with an alcohol use disorder contacted a professional for alcohol problems, the 'treatment gap' may be less problematic than often assumed. That is, those seeking specialized alcohol treatment had the highest persistence rate, whereas those not seeking treatment usually show a favorable course of the disorder and of associated problems. This suggests that efforts to increase treatment access should primarily focus on the small group of non-treatment seekers at high risk of a chronic course; thus particularly those with high levels of drinking and severe alcohol-related problems.

The abovementioned findings have a number of implications for clinical practice and future research. First, the general practitioner and the primary care mental health nurse practitioner (so called POH-GGZ) are key in the recognition and management of alcohol use disorders. Screening for both high levels of drinking and alcohol-related problems is therefore recommended in primary care. Second, this thesis highlights that assessing severity levels of alcohol use disorders and of drinking levels is important to identify who is at risk of a chronic course. Suggestions to optimize care therefore include development of an integrated stepped care approach to provide an optimal match

between disorder severity and treatment intensity. As mostly mild alcohol use disorders were observed in the general population, most people may sufficiently benefit from low-intensity treatment (e.g. e-health interventions; brief motivational interventions with or without pharmacological support) provided in primary care. Yet, timely referral to specialized treatment seems crucial for the small group with a severe or persistent disorder. Third, further research is recommended to examine which interventions are best suitable at which levels of alcohol use problems and to identify cut-offs for structured treatment allocation. To further optimize allocation of care, future research should examine transitions from one severity level of problematic alcohol use to the next. This is also underscored by the findings of this thesis, which showed a gradual nature of alcohol use disorders.

Samenvatting

(Summary in Dutch)

ACHTERGROND

Alcohol speelt een belangrijke rol in onze samenleving: Nederlanders drinken gemiddeld 1 alcoholische consumptie per dag en veel mensen hebben positieve associaties met drinken, ze vinden het bijvoorbeeld gezellig of lekker, of ze drinken als ontspanning. Overmatig gebruik en verslaving kunnen echter tot aanzienlijke problemen voor de gebruiker en zijn/haar omgeving leiden. De kosten van overmatig gebruik en verslaving voor de maatschappij zijn hoger dan van het gebruik van de meeste drugs. Indien een ongezond drinkpatroon resulteert in ernstige beperkingen in het functioneren (bijvoorbeeld op het werk of in de sociale relaties), wordt gesproken van een stoornis in het gebruik van alcohol. Naar schatting hebben een half miljoen Nederlanders jaarlijks te kampen met een dergelijke stoornis. Een ernstige alcoholstoornis kan gepaard gaan met veel ziekte en zelfs leiden tot vroegtijdig overlijden. Het verminderen van het risico op een alcoholstoornis in de algemene populatie zou daarom een prioriteit van de Nederlandse overheid moeten zijn. Om preventie en behandeling goed te kunnen inzetten, is meer informatie nodig over de risicofactoren voor het ontstaan, het beloop en de manier waarop mensen in de algemene bevolking met een alcoholstoornis hulp zoeken. Op dit moment is de meeste kennis hierover afkomstig uit onderzoek in klinische populaties terwijl de meeste mensen met een alcoholstoornis niet in behandeling zijn. Mogelijk zoeken zij geen hulp omdat ze onvoldoende gemotiveerd zijn, maar het zou ook kunnen dat hun problemen relatief mild zijn of omdat ze relatief weinig drinken. Bevindingen uit klinische populaties kunnen daarom niet zomaar geëxtrapoleerd worden naar de algemene bevolking en belangrijke vragen die beantwoord moeten worden zijn:

- Welke mensen hebben een grotere kans op het ontwikkelen van een stoornis in het gebruik van alcohol?
- Hoe hangt deze stoornis in de algemene bevolking samen met excessief drinken?
- Wat bepaalt dat sommige mensen met een stoornis in het gebruik van alcohol in de algemene bevolking herstellen en anderen niet?
- Wordt het zoeken van hulp voor een stoornis in het gebruik van alcohol bepaald door de ernst van de stoornis?

Dit proefschrift onderzoekt deze vragen met gegevens van de 'Netherlands Mental Health Survey and Incidence Study' (NEMESIS-2); een longitudinaal bevolkingsonderzoek met 6.646 volwassenen (18-64 jaar) op de eerste meting en 5.303 bij de vervolgmeting na drie jaar. In deze studie zijn psychische stoornissen, waaronder ook stoornissen in het gebruik van alcohol, gedetailleerd vastgesteld in een representatieve steekproef van de Nederlandse volwassen bevolking.

Beginnen met drinken en ontwikkeling van een alcoholstoornis

Hoofdstuk 2 laat zien dat bijna iedereen ooit in het leven alcohol heeft gedronken (94%), dat de meeste mensen (86%) ooit regelmatig hebben gedronken (≥ 12 drankjes

per jaar), en dat een vijfde van de mensen ooit in het leven een stoornis in het gebruik van alcohol ontwikkelt. Vervolgens zijn in **hoofdstuk 2** twee potentiële risicofactoren voor het ontwikkelen van een alcoholstoornis onderzocht: ADHD in de kindertijd en een gedragsstoornis in de kindertijd. Volwassenen die ADHD in de kindertijd hebben gehad, waren vaker begonnen met drinken en met regelmatig drinken, en zij ontwikkelden vaker een alcoholstoornis. De aanwezigheid van een gedragsstoornis in de kindertijd was een sterke voorspeller van een alcoholstoornis, maar hing niet samen met de eerdere stadia van alcoholgebruik. **Hoofdstuk 2** bevestigt dus de aanwezigheid van een duidelijke associatie tussen ADHD en gedragsstoornis in de jeugd met de aanwezigheid van een stoornis in het gebruik van alcohol in de volwassenheid. Bovendien blijken ADHD en een gedragsstoornis vaak samen voor te komen. Tenslotte blijkt de relatie tussen ADHD en de aanwezigheid van een stoornis in het gebruik van alcohol volledig te worden verklaard door de aanwezigheid van een gedragsstoornis. De oplopende leeftijden waarop ADHD, gedragsstoornis en alcoholstoornis ontstaan (respectievelijk 7, 12 en 19 jaar) suggereren een ontwikkelingsmechanisme van ADHD naar gedragsstoornis en vervolgens naar alcoholstoornissen. Vroege interventies bij kinderen met ADHD zouden kunnen helpen een latere gedragsstoornis en daarmee ook een latere stoornis in het alcoholgebruik te voorkomen. Aandacht voor alcoholgebruik bij de behandeling van kinderen met ADHD of een gedragsstoornis zou de kans op alcoholstoornissen wellicht verder kunnen verkleinen.

De samenhang tussen excessief drinken en een alcoholstoornis

Hoewel het logisch lijkt dat excessief drinken een vereiste is voor een diagnose van een stoornis in het gebruik van alcohol, laat **hoofdstuk 3** slechts een zwakke samenhang zien: slechts 18% van de mensen met een alcoholstoornis drinkt excessief. Excessief drinken is in dit hoofdstuk vrij streng gedefinieerd als zowel een hoge gemiddelde consumptie als frequent binge drinken (5 of meer drankjes bij één gelegenheid). Maar ook met minder strenge definities is een vergelijkbare beperkte samenhang zichtbaar. Om deze beperkte samenhang beter te begrijpen, zijn drie groepen problematische drinkers (alléén excessief drinken, alléén alcoholstoornis, beide) vergeleken met niet-problematische drinkers op demografie, mentale gezondheid, functioneren en zorggebruik. Vergeleken met niet-problematische drinkers, werd in alle drie de groepen problematische drinkers meer psychopathologie (depressie, angst en drugverslaving; ADHD in de kindertijd) en een verminderd functioneren gevonden. Al deze subgroepen lijken dus klinisch relevante pathologie te vertegenwoordigen. Degenen bij wie beide aspecten van problematisch alcoholgebruik aanwezig zijn (excessief drinken en een alcoholstoornis) lijken het meest kwetsbaar en zij hebben het vaakst een angststoornis, suïcide gedachten en/of een antisociale persoonlijkheidsstoornis. **Hoofdstuk 3** laat ook zien dat respondenten in deze laatste subgroep vaker een laag opleidingsniveau en/of een laag inkomen hebben en dat ze vaker alleen wonen. In combinatie met resultaten uit eerder prospectief onderzoek, suggereren deze bevindingen dat deze kenmerken

kunnen helpen om mensen met een hoog risico op ernstige alcoholproblematiek te herkennen. De resultaten uit **hoofdstuk 3** wijzen erop dat het voor het onderzoeken en behandelen van problematisch alcoholgebruik belangrijk is dat met beide aspecten (excessief drinken én alcoholstoornis) rekening wordt gehouden.

Beloop

Hoofdstuk 4 laat zien dat alcoholstoornissen in de algemene bevolking vaak een gunstig beloop kennen: 70% herstelt binnen 3 jaar. Dit hoge herstelpercentage moet echter wel met de nodige voorzichtigheid worden geïnterpreteerd: meer dan een derde van de groep in diagnostische remissie drinkt nog steeds substantieel (meer dan 7 drankjes per week voor vrouwen of meer dan 14 drankjes per week voor mannen). Bepaalde klinische kenmerken (bijvoorbeeld een groter aantal symptomen, meer beperkingen als gevolg van de stoornis en meer alcoholgebruik) bleken voorspellers van een chronisch beloop van de alcoholstoornis. Sociodemografische kenmerken, roken, comorbide depressie, drugsverslaving en kwetsbaarheidsfactoren (ouderlijke psychopathologie, traumatisering als kind) bleken niet geassocieerd met een chronisch beloop. Een comorbide angststoornis is echter wel een onafhankelijke voorspeller van chroniciteit. Samen verklaren deze factoren slechts een kwart van de variantie in de persistentie van een aanwezige alcoholstoornis en dus moeten er nog andere factoren zijn, hier niet onderzocht, die een rol spelen.

Hoofdstuk 5 laat zien dat terugval na aanvankelijke diagnostische remissie van een alcoholstoornis zeldzaam is in de algemene bevolking. Slechts 12% van de mensen in diagnostische remissie ontwikkelde binnen 3 jaar opnieuw een alcoholstoornis. **Hoofdstuk 5** laat verder zien dat de aanwezigheid van meer criteria voor de diagnose alcoholstoornis (≥ 6 criteria van alcoholstoornis ooit in het leven) en meer alcoholgebruik (wekelijks meer dan 14/21 drankjes voor vrouwen/mannen) onafhankelijke voorspellers zijn van terugval. Daarnaast blijkt dat overmatig drinken tijdens remissie (wekelijks meer dan 7/14 drankjes voor vrouwen/mannen) de kans op terugval sterk verhoogt, vooral bij mensen die in het verleden voldeden aan veel criteria van de alcoholstoornis en erg veel dronken. Dit duidt erop dat aandacht voor drinkpatronen tijdens remissie van belang is voor behandeling en terugvalpreventie. Met name mensen met een geschiedenis van ernstige alcoholproblematiek hebben mogelijk baat bij abstinentie of een erg laag niveau van alcoholgebruik. Gecontroleerd drinken op een hoger niveau lijkt alleen een optie bij degenen zonder een geschiedenis van ernstige problematiek of in combinatie met medicatie.

Zorggebruik

Hoofdstuk 6 laat zien dat slechts 10% van de mensen met een alcoholstoornis in de algemene bevolking gedurende vier jaar hulp zocht voor hun alcoholproblemen. Een derde (35%) zocht hulp voor andere emotionele of drugsproblemen en meer dan de helft van de mensen met een alcoholstoornis zocht of kreeg geen professionele hulp

in een periode van vier jaar. Deze cijfers suggereren het bestaan van een aanzienlijke 'behandelkloof'. Uit dit proefschrift blijkt verder dat mensen die behandeling ontvangen voor hun alcoholproblemen gemiddeld meer symptomen en meer beperkingen als gevolg van de alcoholstoornis hebben en vaker een comorbide stemmings- of angststoornis hebben dan mensen met een alcoholstoornis die hiervoor geen hulp zoeken. Degenen die hulp ontvangen voor andere emotionele problemen of drugsproblemen hebben vaker een comorbide stemmings- of angststoornis dan mensen die helemaal geen hulp ontvangen. Ten opzichte van mensen die hulp zochten voor hun alcoholstoornis, vertonen mensen die geen hulp ontvangen en mensen die hulp ontvangen voor andere emotionele problemen een veel beter beloop met veel hogere herstelpercentages: 78% en 64% versus slechts 29%. Dit lijkt te duiden op adequaat hulpzoekgedrag: degenen met een chronisch beloop zoeken vaker professionele hulp voor hun alcoholproblemen. Tot slot werd gevonden dat het functioneren van de mensen met een alcoholstoornis die helemaal geen zorg hadden ontvangen na drie jaar vergelijkbaar was met het functioneren van een gezonde vergelijkingsgroep: mensen die op de nulmeting nog nooit een alcoholstoornis hadden gehad en die ook geen andere psychische stoornis hadden. Dit wijst erop dat de onvervulde zorgbehoefte waarschijnlijk beperkt is tot de groep mensen zonder zorg met een persistente stoornis (22% van de mensen die geen hulp ontvangen). Samenvattend lijkt de 'behandelkloof' minder problematisch dan vaak wordt verondersteld: mensen die de zorg het meest nodig hebben lijken de weg naar de verslavingszorg redelijk goed te vinden en degenen die geen zorg krijgen hebben over het algemeen milde problemen en een gunstig beloop.

DISCUSSIE

Bijna iedereen heeft ooit in het leven alcohol gedronken en ongeveer een vijfde van de Nederlandse volwassenen ontwikkelt ooit in het leven een alcoholstoornis. Daarbij hebben volwassenen die een externaliserende stoornis in de kindertijd hebben gehad vaker een alcoholstoornis: ADHD in de kindertijd lijkt via de ontwikkeling van gedragsstoornis te kunnen leiden tot een alcoholstoornis in de volwassenheid. Dit betekent dat de vroegtijdige herkenning en behandeling van deze externaliserende stoornissen in de kindertijd mogelijk kan bijdragen aan het voorkomen van latere alcoholstoornissen.

Opmerkelijk is dat de meeste mensen met een stoornis in het gebruik van alcohol in de algemene bevolking milde en voorbijgaande problemen hebben: 75-80% drinkt niet excessief, 70% herstelt binnen drie jaar en slechts 12% van de mensen in diagnostische remissie recidiveert. Het lijkt daarom efficiënt om behandeling van de stoornis vooral in te zetten op die mensen die een vergroot risico hebben op een ernstige en/of chronische stoornis: degenen met een hoog drinkniveau, veel alcoholsymptomen en comorbide psychopathologie, met name angststoornissen.

Ondanks dat slechts 10% van de mensen met een alcoholstoornis hulp zocht voor deze problemen, lijkt de 'behandelkloof' minder problematisch dan vaak wordt verondersteld. De mensen die wel hulp zochten voor hun alcoholproblemen hadden meestal een chronisch verlopende aandoening, terwijl degenen die geen hulp ontvingen juist een gunstig beloop hadden. Dit wijst erop dat pogingen om de toegang naar behandeling van alcoholproblemen te vergemakkelijken zich vooral zouden moeten richten op risicogroepen: degenen met een hoog drinkniveau en ernstige alcohol gerelateerde problemen.

Deze bevindingen hebben een aantal implicaties voor de klinische praktijk en voor toekomstig onderzoek. Allereerst spelen de huisarts en de POH-GGZ in toenemende mate een cruciale rol in de herkenning van alcoholstoornissen. Dit pleit voor screening in de huisartsenpraktijk met daarbij aandacht voor zowel de mate van alcoholgebruik als voor het aantal symptomen van een alcoholstoornis. Ten tweede benadrukt dit proefschrift dat het meten van ernstniveaus van de alcoholstoornis en van drinkpatronen van belang is om de kleine groep met een ernstig beloop te herkennen. Suggesties voor verbetering van zorg omvatten daarom ook de ontwikkeling van een 'stepped care' benadering voor behandeling, waarbij de ernst van de alcoholproblematiek (hoeveel alcohol, aantal symptomen) en de intensiteit van de behandeling goed op elkaar kunnen worden afgestemd. Het grote aantal mensen met een milde alcoholstoornis in de algemene bevolking heeft in veel gevallen voldoende baat bij interventies met een (relatief) lage intensiteit (bijvoorbeeld e-health interventies of korte motiverende gespreksvoering met of zonder medicamenteuze ondersteuning) verleend in de huisartsenpraktijk. Daarentegen lijkt tijdige verwijzing van groot belang voor de kleine groep met een ernstige en/of chronische alcoholstoornis. Nadere bestudering van de overgang van het ene ernstniveau van alcoholproblematiek naar het volgende is nodig voor een juiste toewijzing van zorg. Dit belang wordt onderschreven door dit proefschrift waarin het geleidelijke karakter van alcoholproblematiek duidelijk naar voren komt.

Dankwoord

(Acknowledgements)

DANKWOORD

Bij het schrijven van dit proefschrift heb ik een team van geweldige (co)promotoren om me heen gehad: Wim, Wilma, Margreet en Ron. Alle vier zijn jullie wetenschappers van formaat met een enorme expertise, ik voel me bevoorrecht dat jullie mij in dit proces hebben begeleid. Wim, jouw onuitputtelijke kennis en enthousiasme vormen een fantastische mix en je hebt mij keer op keer het vertrouwen gegeven dat ik op weg was iets moois af te leveren. Wilma, jij keek met een frisse blik naar mijn stukken en kon daardoor feilloos aanwijzen waar ik een denkstap oversloeg of er onterecht van uitging dat iets algemene kennis was. Ron en Margreet, jullie vormden samen de perfecte combinatie. Waar Ron in zijn reacties (ook op afstand!) altijd het overzicht bewaarde en de zwakke plekken van een stuk helder kon weergeven, vulde Margreet dit aan met haar precieze blik zodat uiteindelijk alle puntjes op de i stonden. Bovendien was NEMESIS-2 er niet geweest zonder jullie tomeloze inzet. Ik heb de afgelopen jaren erg veel van jullie geleerd en ben jullie zeer dankbaar voor de kansen die jullie me gegeven hebben.

Natuurlijk gaat mijn dank ook uit naar de 6.646 deelnemers van NEMESIS-2. Dankzij jullie geeft dit proefschrift een uniek inzicht in alcoholstoornissen en kan het daardoor bijdragen aan betere preventie en zorg. Ook wil ik alle interviewers en hun begeleiders bij het veldwerkbureau GfK bedanken: jullie inzet heeft geresulteerd in een prachtige dataset!

Peggy, na ruim een jaar zijn de rollen omgedraaid en ben jij mijn paranimf. Met jouw energie en liefde voor onderzoek ben je de afgelopen jaren een voorbeeld voor me geweest. Maar niet alleen dat, je was ook een trouwe meelezer, sparring-partner, mental coach, (borrel)maatje en laten we eerlijk zijn, anonieme co-auteur. Mijn dank is immens groot en ik ben blij dat je straks naast me wilt staan! Nina, we zijn al sinds de brugklas bevriend en jij was degene die mij er dik vijf jaar geleden op wees dat het Trimbos misschien leuke vacatures had. Je hebt dus in feite de basis gelegd voor dit geheel. Daarnaast heb ik de afgelopen jaren lief en leed met je kunnen delen tijdens de vele lunch- en theepauzes op het Trimbos, maar zeker ook daarbuiten. Ik ben je heel dankbaar dat je altijd voor me klaarstaat en dat je mijn paranimf wilt zijn.

Saskia, mijn kamergenoot en 'drill instructor' op het gebied van data-cleaning en -analyse. Al vrij snel na mijn eerste werkdag werd ik gewaarschuwd dat niemand het bij je volhield op de kamer. Ik kan me echter geen betere kamergenoot voorstellen en hoop dat we samen nog lang door kunnen als Statler en Waldorf! Bedankt voor de ontelbare keren dat je 'even' hebt meegekeken, maar zeker ook voor je peptalks, interesse en de lol die we samen hebben. Daarnaast wil ik de andere collega's van Epidemiologie & Research support graag bedanken. Marloes, als programmahoofd stimuleer je me om mezelf verder te ontwikkelen en over drempels heen te stappen. Jouw vertrouwen en ondersteuning helpen mij daar zeker bij. Karin, ik moet vaak enorm lachen om jouw 'domme' vragen en zeker op stille dagen waren die vragen een fijn

excuus om even te pauzeren en bij te praten. Jacqueline, ik vind het knap hoe jij altijd de kalmte weet te bewaren en jouw relativerende opmerkingen hebben me geholpen de dingen in perspectief te plaatsen. Evelien, toen ik binnenkwam bij het Trimbos werd jij aangewezen als mijn mentor en heb je me wegwijs gemaakt. Nog steeds kan ik altijd bij je terecht (zelfs nu je officieel niet meer bij 'epi' hoort) en dat waardeer ik enorm. Jasper, ik bewonder jouw stressbestendigheid en ik vond het een voorrecht om vorig jaar met je samen te werken voor de trendrapportages. Ellen, het maakte niet uit welke klus ik voor je had bedacht, je was altijd enthousiast en deed het heel secuur, dank daarvoor. Yvonne, Harry en Nancy, jullie vertegenwoordigen sinds kort de 'Research support'-tak van ons programma, ik hoop veel van jullie te kunnen leren!

Los van mijn programma wil ik nog een aantal (ex-)collega's bedanken. Anouk en Froukje, ik waardeer het zeer dat jullie altijd, zelfs tijdens verhuizingen, de tijd vonden om mijn stukken te lezen. Marja, ondanks je overstap naar een ander programma ben je interesse blijven tonen in mijn ontwikkeling en in de afronding van dit proefschrift. Een deel van dit proefschrift heb ik geschreven op het AMC, en ook daar voelde ik me altijd gesteund. Bep en Marianne, jullie wisten als geen ander om te gaan met (wijzigingen in) het promotiereglement en alles wat daarbij komt kijken. Maarten, jij bent een grootheid op het gebied van statistiek. Mark Bench en de rest van de AIAR journal club: dank voor jullie luisterend oor, kritische blik en adviezen!

Lieve vrienden en (schoon-)familie, zonder jullie had ik het nooit gered en jullie zijn me zeer dierbaar. Een aantal mensen wil ik in het bijzonder bedanken. Jiska, Nina en Tanja, voor het eerst in ruim 10 jaar wonen we weer op een steenworp afstand van elkaar. Dat maakt afspreken een stuk makkelijker dus wat mij betreft wordt er nu niet meer verhuisd! Sanne, onze traditie om series te kijken hebben we na Maastricht gelukkig kunnen volhouden, al moeten we er soms helemaal voor naar de Spaanse zon. Femke, Joris, Menno en Rick. De theatervoorstellingen, weekendjes weg, etentjes en andere legendarische activiteiten deden me mijn proefschriftstress altijd even vergeten. Jan en Ria, jullie vertrouwen en onvoorwaardelijke steun hebben me gebracht waar ik nu ben, ik kan jullie daar niet genoeg voor bedanken. En tot slot, Mike. Dat jij het deze periode, en vooral het afgelopen jaar, met mij hebt volgehouden is een wonder. Dank voor alles. Ik kan met niemand zo goed relaxen en lachen als met jou, en dat gaan we nu weer vaker doen. Si.

Marlous

About the author

CURRICULUM VITAE

Marlous Tuithof was born on October 2nd, 1985 in Maarssen, the Netherlands. She graduated from secondary school at the St. Antonius college in Gouda in 2004. In that same year she moved to Limburg for the bachelor Health Sciences at Maastricht University, specializing in Psychological Health Sciences. Her bachelor was complemented with an honors track, which involved studying the role of childhood adversities in borderline personality disorder. She graduated Cum Laude (2007) and pursued a master's degree at the Graduate School of Social and Behavioral Science of Utrecht University. During the research master program Psychological Health Research her taste for research grew stronger and she conducted research varying from web surveys to experimental studies as part of her training. After graduating in 2009, she was employed as a research associate at the Trimbos Institute (Netherlands Institute of Mental Health and Addiction, Utrecht) and joined the NEMESIS-2 research team. She was involved in the data collection of the second and third wave of this unique longitudinal population-based study. Additionally, she conducted research on some of the various topics that are available in the NEMESIS-2 data. Published topics include informal caregiving, ADHD, and alcohol use disorders; the results of her studies considering alcohol use disorders are described in this thesis. She still holds a position with the Epidemiology & Research support department at the Trimbos Institute.

PORTFOLIO

PhD period	March 2010 – February 2015
Position	External candidate
Supervisors	Prof. dr. W. van den Brink and prof. dr. W.A.M. Vollebergh
Co-supervisors	Dr. M.L. ten Have and dr. ir. R. de Graaf

PhD Training	**Year**	**ECTS**
Courses		
Writing grant proposals	2015	0.3
Computing in R	2013	0.4
Professional presenting	2012	0.8
The Big Mplus Show	2011	1.5
Longitudinal data analysis	2011	0.5
Imputing missing values	2011	0.3
Project management	2010	0.3
Seminars, workshops and master classes		
Journal club (department of Psychiatry)	2013-2015	2.0
Oral presentations		
Zorggebruik voor alcoholstoornissen		
Forum Alcohol en Drugs Onderzoek (FADO), Utrecht	2014	0.75
Alcohol consumption and symptoms as predictors for relapse of DSM-5 alcohol use disorder		
Section meeting of the European Psychiatric Association (EPA), Ulm	2014	1.0
Risk indicators of mood and anxiety disorders among informal caregivers		
Section meeting of the European Psychiatric Association (EPA), Ulm	2014	0.75
Risico-indicatoren voor stemmings- en angststoornissen bij mantelzorgers		
Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie (NVvP), Maastricht	2014	0.5

Het voorspellen van recidiverende alcoholstoornissen in de algemene bevolking		
Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie (NVvP), Maastricht	2014	0.5
Forum Alcohol en Drugs onderzoek (FADO), Utrecht	2013	0.75
The relationship between excessive alcohol consumption and alcohol use disorders		
Conference of the European Association of Substance Abuse Research (EASAR), Nijkerk	2012	1.25
Welke rol speelt gedragsstoornis in de associatie tussen ADHD en (stoornissen in) alcoholgebruik?		
Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie (NVvP), Maastricht	2012	0.5
Forum Alcohol en Drugs Onderzoek (FADO), Utrecht	2011	0.75
ADHD, gedragsstoornissen en antisociale persoonlijkheidsstoornis. Vóórkomen en gevolgen in de algemene bevolking: resultaten van NEMESIS-2		
Ministerie van Volksgezondheid, Welzijn en Sport (VWS), Den Haag	2011	0.5

PUBLICATIONS

In this thesis

Tuithof M, ten Have M, van den Brink W, Vollebergh W, de Graaf R. The role of conduct disorder in the association between ADHD and alcohol use (disorder). Results from the Netherlands Mental Health Survey and Incidence Study-2. *Drug and Alcohol Dependence* 2012; 123: 115-121.

Authors' contributions: MtH and RdG obtained funding for data collection and for the research described in this publication. They also contributed to acquisition of data. MT undertook the analyses and wrote the first draft of the manuscript. All authors contributed to the conception, design and interpretation of analyses for the manuscript as well as its critical revision. All authors contributed to and have approved the final manuscript. No conflicts of interests were declared.

Tuithof M, ten Have M, van den Brink W, Vollebergh W, de Graaf R. Predicting persistency of DSM-5 alcohol use disorder and examining drinking patterns of recently remitted individuals: a prospective general population study. *Addiction* 2013; 108: 2091-2099.

Authors' contributions: MtH and RdG obtained funding for data collection and for the research described in this publication. MT, MtH and RdG contributed to acquisition of data. MT undertook the analyses and wrote the first draft of the manuscript. All authors contributed to the conception, design and interpretation of analyses for the manuscript as well as its critical revision. All authors contributed to and have approved the final manuscript. No conflicts of interests were declared.

Tuithof M, ten Have M, van den Brink W, Vollebergh W, de Graaf R. The relationship between excessive alcohol consumption and alcohol use disorders according to DSM-IV and DSM-5. *Alcoholism: Clinical and Experimental Research* 2014; 38: 249-256.

Authors' contributions: MtH and RdG obtained funding for data collection and for the research described in this publication. They also contributed to acquisition of data. MT undertook the analyses and wrote the first draft of the manuscript. All authors contributed to the conception, design and interpretation of analyses for the manuscript as well as its critical revision. All authors contributed to and have approved the final manuscript. No conflicts of interests were declared.

Tuithof M, ten Have M, van den Brink W, Vollebergh W, de Graaf R. Alcohol consumption and symptoms as predictors for relapse of DSM-5 alcohol use disorder. *Drug and Alcohol Dependence* 2014; 140: 85-91.

Authors' contributions: MtH and RdG obtained funding for data collection and for the research described in this publication. MT, MtH and RdG contributed to acquisition of data. MT undertook the analyses and wrote the first draft of the manuscript. All authors contributed to the conception, design and interpretation of analyses for the manuscript as well as its critical revision. All authors contributed to and have approved the final manuscript. No conflicts of interests were declared.

Tuithof M, ten Have M, van den Brink W, Vollebergh W, de Graaf R. Treatment seeking for alcohol use disorders: treatment gap or adequate self-selection? *Under review*.

Authors' contributions: MtH and RdG obtained funding for data collection and for the research described in this publication. MT, MtH and RdG contributed to acquisition of data. MT undertook the analyses and wrote the first draft of the manuscript. All authors contributed to the conception, design and interpretation of analyses for the manuscript as well as its critical revision. All authors contributed to and have approved the final manuscript. No conflicts of interests were declared.

Other publications

Tuithof M, ten Have M, van Dorsselaer S, de Graaf R. ADHD, gedragsstoornissen en antisociale persoonlijkheidsstoornis. Vóórkomen en gevolgen in de algemene bevolking: resultaten van NEMESIS-2. Utrecht. Trimbos-instituut, 2010.

Tuithof M, ten Have M, van Dorsselaer S, de Graaf R. Prevalentie, persistentie en gevolgen van ADHD in de Nederlandse volwassen bevolking. *Tijdschrift voor Psychiatrie.* 2014; 56: 10-19.

Tuithof M, ten Have M, van Dorsselaer S, de Graaf R. Emotional disorders among informal caregivers in the general population: target groups for prevention. *BMC Psychiatry*. 2015; 15: 23.

Tuithof M, ten Have M, van Dorsselaer S, de Graaf R. Risico-indicatoren van emotionele stoornissen bij mantelzorgers. Resultaten van NEMESIS-2. *Under review*.

Co-authored

Batelaan N, ten Have M, van Balkom A, **Tuithof M**, de Graaf R. Anxiety disorders and onset of cardiovascular disease: the differential impact of panic, phobias and worry. *Journal of Anxiety Disorders* 2014; 28: 252-258.

Boumans J, **Tuithof M**, van Hoof F, Nuijen J. Hoofdbehandelaarschap en kwaliteit van zorg. Perspectieven van GGZ-cliënten. Utrecht, Trimbos-instituut, 2014.

De Graaf R, **Tuithof M**, van Dorsselaer S, ten Have M. Comparing the effects on work performance of mental and physical disorders. *Social Psychiatry and Psychiatric Epidemiology*. 2012; 47: 1873-1883.

De Graaf R, ten Have M, **Tuithof M**, van Dorsselaer S. Incidentie van psychische aandoeningen. Opzet en eerste resultaten van de tweede meting van de studie NEMESIS-2. Utrecht, Trimbos-instituut, 2012.

De Graaf R, **Tuithof M**, van Dorsselaer S, ten Have M. Verzuim door psychische en somatische aandoeningen bij werkenden. *Tijdschrift voor Arbeidsvraagstukken*. 2013; 29: 322-337.

De Graaf R, van Dorsselaer S, **Tuithof M**, ten Have M. Sociodemographic and psychiatric predictors of attrition in the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). *Comprehensive Psychiatry*. 2013; 54: 1131-1139.

De Graaf R, ten Have M, **Tuithof M**, van Dorsselaer S. First-incidence of DSM-IV mood, anxiety and substance use disorders and its predictors: results from the Netherlands Mental Health Survey and Incidence Study-2. *Journal of Affective Disorders* 2013; 149: 100-107.

Nuijen J, ten Have M, **Tuithof M**, van Dorsselaer S, van Bon-Martens M, de Graaf R. Trendrapportage GGZ: Geen gebruik van professionele zorg bij stemmings- en angststoornissen: zorgelijk of niet? Utrecht, Trimbos-instituut, 2014.

Ten Have M, van Dorsselaer S, **Tuithof M**, de Graaf R. Nieuwe gegevens over suïcidaliteit in de bevolking. Resultaten van NEMESIS-2. Utrecht, Trimbos-instituut, 2011.

Ten Have M, van Weeghel J, van Dorsselaer S, **Tuithof M**, de Graaf R. Houding van de algemene bevolking ten opzichte van (ex-) psychiatrische patiënten; resultaten van de Netherlands Mental Health Survey and Incidence Study-2. *Under review*.